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(54) **IMMUNODOMINANT HUMAN T-CELL EPITOPES OF HEPATITIS C VIRUS**

VON MENSCHLICHEN T-ZELLEN IMMUNODOMINANTE EPIROPEN DES VIRUS DER C-HEPATITIS

EPITOPES DE LYMPHOCYTES T HUMAINS IMMUNODOMINANTS DU VIRUS DE L'HEPATITE C

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(73) Proprietor: **INNOGENETICS N.V.**
9052 Ghent (BE)

(72) Inventors:
- **LEROUX-ROELS, Geert**
  B-9000 Ghent (BE)
- **DELEYS, Robert**
  B-1850 Grimbergen (BE)
- **MAERTENS, Geert**
  B-8310 Brugge (BE)

(74) Representative: **De Clercq, Ann**
De Clercq, Brants & Partners cv.,
Edgard Gevaertdreef 10a
9830 Sint-Martens-Latem (BE)

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- **JOURNAL OF VIROLOGY, vol.67, no.12, December 1993 pages 7522 - 7532 KOZIEL, M. J. ET AL. 'Hepatitis C Virus (HCV)-specific cytotoxic T lymphocytes recognize epitopes in the core and envelope proteins of HCV'**

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Description

[0001] The present invention describes immunodominant hepatitis C virus T cell epitopes useful in hepatitis C prophylactic and therapeutic vaccines, derived from the HCV core, protein.

Technical field of the invention

[0002] The present invention relates to the production of novel synthetic immunogens reteted to the hepatitis C virus core region and to the use thereof in the production of vacclnes, therapeutic egents end the like. More specifically, the present invention relates to polypeptide compositions containing HCV core, T cell determinants.

Background of the invention

[0003] In the few years since its discovery, Hepatitis ·C virus (HCV) has been shown to be a major cause of acute end chronic liver disease. HCV is a single-stranded RNA virus with a genome of approximately 9400 nucleotides that consists of a 5' untranslated region (5'UR) of 341 nucleotides which precedes a single large open reading frame encoding a precursor polyprotein of ebout 3010 amino acids (Kato et al., 1990). The genetic organizatlon of the virel genome is related to that of flavi-and pestiviruses, with the putative structural proteins located in the N-terminal region and a variety of non structural proteins located et the C-terminal end of the polyprotein. The structural proteins are the core protein (C, amino acids 1-191) followed by the putative envelope proteins E1 (amino acids 192-383) and E2/NS1 (amino acids 384-746). The terms E2 and NS1 are often used interchangeably. Another form of E2 is composed of amino acids 384 to 809 and a third form is associated with NS2. The non structural proteins are NS2, NS3, NS4 and HS5, of which at least NS4 and MS5 have been shown to be further processed into HS4A, NS4B, NS5A, and NS5B.

[0004] Structural analysis of HCV genomes revealed the existence of different genotypes that have been classified into types and subtypes (Stuyver et al., 1993). The sequence diversities are distributed along the whole genome including the 5' untranslated region. The highest sequence variability has been observed in the NS2 and 3' untranslated regions, and in the putative envelope regions encoding the E1 and E2 proteins. The core, NS3, and certain regions of the NS4 proteins displayed markedly less diversity (Okamoto et al., 1992).

HCV humoral response

[0005] Soon after the discovery of HCV, immunoassays for the detection of circulating antibodies against HCV proteins became widely available. These tools have led to an explosive increase of the knowledge in the field of the human humoral immune response to HCV in different conditions. Once it was demonstrated that HCV was the major cause of posttransfusional non-A, non-B hepatitis, the search for entibodies to HCV was added to the safety screening panel of blood products. This procedure not only increased the safety of blood transfusions but also enhanced the knowledge of the epidemiology of the virus. The fact that HCV is responsible for a large proportion of chronic hepatic infections in which blood transfusion or parenteral inoculation are excluded remains a major challenge for further epidemiological studies. The widespread use of the assays for the detection of antibodies to HCV has also led to the recognition of the regions with humoral antigenicity of the virus. The relationship between the kinetics and magnitude of the humoral immune response to the different proteins of HCV and the course and outcome of the disease remains to be established.

HCV T cell epitopes

[0006] The immune response to viral antigens is almost entirely T cell dependent. T cells are required both for entibody production and for some cytotoxlc reactions. HCV-encoded proteins are immunogenic not only at the B cell level, but also at the T cell level.

[0007] Studies describing the cellular immune response to HCV are scarce. Lln et al. (1993) describe candidate T cell epitopes within absolutely conserved regions of HCV gene obtained by means of a computer search revealing e large number of potentiel T cell epitopes. It has also been reported that peripheral blood cell monocytes (PBMC) from HCV-infected individuels proliferate in response to HCV recombinant proteins and that peripheral responses to core protein correlate with a benign course of infection (Botarelli et el., 1993). In the liver of patients with chronic HCV infection HCV-specific, HLA class I- restricted cytotoxic T lymphocytes (CTL) have been identified and cloned that recognlze epitopes in E1 end NS2 proteins. These investigators have mainly focused on obtaining T cell clones from individual patients, and on the localization of the immunoreactive domain for the single CTL clones. Such studies led to the discovery of the epitope ASRCWVAM (aa 235-242) In the aminoterminal part of the E1 protein, and of the epitope LMALTLSPYYKRY (aa 826-838) from the NS2 region (Kozlel et al., 1992). In patients with chronic HCV hepatitis intrehepatic $CD4^+$ T cells which specifically recognized the NS4 proteln of HCV were observed. The clonotype of these

T lymphocytes was not detectable in the PBMC from these subjects (Minutello et al., 1993). These studies demonstrate that in patients with HCV hepatitis, HCV-specific T lymphocytes can be isolated from the infected liver end the peripheral blood. Their role in the pathogenesis of the liver damage in HCV hepatitis end their relevance for the clearance or persistence of the virus remains to be established.

[0008] Although neutralization of certain viral infections is possible by humoral immunity only, most microbiological agents can only be cleared from the host with the aid of cellular immunity. Even when the neutralizing capacity of circulating antibodies is esteblished in certain infections, T helper cell activity is generally required to allow B cells to produce the required levels of circulating entibodies, for achievement of neutralizetion and clearance of the infectious agent. However, certein infectious agents can only be neutralized by means of cellular immunity.

[0009] In the case of hepatitis C virus, it can be anticipated that T cell immunity may be required for clearance of the virus, since most patients enter into a chronic course of the disease, and since most patients infected with HCV have developed humoral immunity to most of the HCV antigens which can be employed'for diagnosis of HCV infection, as described in patent epplications no. EP-A-0 318 216, EP-A-0 388 232, EP-A-0 442 394, EP-A-0 484 787, EP-A-0 489 968. However, most of the antibody-positive patients have not been able to clear the virus from the circuletion since they remain HCV-PCR positive end, consequently, the detected antibodies have not been protective neither sufficient to neutralize the virus. Possibly, antibodies to other epitopes which ere currently not included in HCV diagnostic assays may be capable of neutralizing HCV infection. Such epitopes mey be loceted on the viral membrane proteins E1 and E2, but protection against a wide range of different HCV species may be hampered by the hypervariability of HCV envelope regions.

[0010] The aim of the present invention is to provide T cell stimulating polypeptides and peptides derived from the HCV structural region.

[0011] Another aim of the present invention is to provide T cell stimulating polypeptides and peptides as defined above for use in the preparation of en HCV immunogenic composition.

[0012] Another aim of the present invention is to provide T cell stimulating peptides or polypeptides derived from the core region, of HCV.

[0013] Another aim of the present invention is to provide T cell stimulating peptides or polypeptides from HCV as specified above which contain either T helper cell ($CD4^+$) epitopes and/or CTL ($CD8^+$) epitopes.

[0014] Another aim of the present invention is to provide recombinent polypeptides containing the same.

[0015] Another aim of the present invention is to provide therapeutic as well es prophylactic compositions comprising the same.

[0016] Another aim of the present invention is to provide prophylactic or therapeutic compositions comprising said polypeptides.

[0017] Another aim of the present invention is to provide methods for preventing or treating HCV infection based on the same.

Detailed description of the invention

[0018] More particularly, the present invention describes a polypeptide of about 8 to about 20 amino acids comprising or consisting of at least 8 contiguous amino acids selected from the core region of the HCV polyprotein, with said contiguous amino acids containing a T-cell stimulating epitope, and provided that said polypeptide is different from any known T cell epitope containing HCV peptide or polypeptide described from any of the above-mentioned regions. The latter known HCV polypeptides and peptides are described for screening for B cell epitopes. Such polypeptides and peptides are for instance mentioned in EP-A-0 318 216, BP-A-O 388 232, EP-A-0 442 394, EP-A-0 484 787, EP-A-0 489 968, WO 92/22571, Lesniewski et al., 1993; Weiner et al., 1993; etc. The content of these applications is hereby incorporated by reference.

[0019] Even more particularly, the present invention relates to the use of polypeptides as described above for the preparetion of an HCV immunogenic composition.

[0020] The expression "HCV immunogenic composition" refers to the prevention or treatment of HCV infection.

[0021] Preferentially said polypeptide is different from RALAHGVRVLEDG.

[0022] The term "HCV polyprotein" refers to any HCV polyprotein disclosed in the art and is reviewed in Okamoto et al. 1992, such es the type 1a HCV polyprotein of the HC-J1 isolate, such es the HCV polyprotein of the type 2a HC-J6 isolate (Okamoto et el., 1991), the type 2b HC-J8 isolate (Okamoto et al., 1992). According to this definition, any variation elready observed within any of the described regions of HCV Is to be considered as part of the definition of HCV polyprotein. For example, numerous types and subtypes are disclosed in Bukh et al., 1993, Bukh et al., 1994, Stuyver et al., 1993a, Stuyver et al., 1993b, Stuyver et el., 1994a, Stuyver et al., 1994c. Moreover, conservative substitutions may be introducad In these HCV polyproteins according to the present invention. The term "conservative substitution" es used herein denotes that one amino acid residue has been replaced by another, biologically similar residue. Examples of conservative substitutions include the substitution of one hydrophobic residue such as Isoleucine,

valine, leucine or methionine for another, or the substitution of one polar residue for another such as between arginine and lysine, between glutamic and aspartic acids or between glutamine and asparagine and the like. The term "conservative substitution" also includes the use of a substituted amino acid in place of an unsubstituted parent amino acid provided that antibodies raised to such a polypeptide also immunoreact with the corresponding polypeptide having the unsubstituted amino acid.

[0023] The term "antibody" refers to a molecule that is a member of a family of glycosylated proteins called immunoglobulins. which can specifically combine with en entigen.

[0024] The word "antigen" has been used historically to designate en entity that is bound by an antibody, and also to designate the entity that induces the production of the entibody. More current usage limits the meaning of antigen to that entity bound by an antibody, while the word "immunogen" is used for the entity that induces antibody production. Where an entity discussed herein is both immunogenic and antigenic, reference to it as either an immunogen or antigen will typically be made eccording to its intended utility.

[0025] The term "corresponds" in its verious grammatical forms as used in relation to peptide sequences means the peptide described plus or minus up to three amino acid residues et either or both of the amino- and carboxy-termini and containing only conservative substitutions in particular amino acid residues along the polypeptide sequence.

[0026] "Epitope" refers to that portlon of a molecule that is specifically bound by a T cell antigen receptor or an antibody combining site.

[0027] The term "immunoreact" in its various forms means binding between an antigen es a ligand and a molecule conteining an antibody combining site such as a Fab portion of a whole antibody.

[0028] The expression "T-cell stimulating epitope" or T cell epitope according to the present invention refers to en epitope capable of stimulating T-cells. A T-cell stimulating epitope may be selected according to the present invention by monitoring the lymphoproliferative response (es detailed in the Examples section) towards polypeptides containing in their amino acid sequence at least 8 contiguous emino acids derived from the core region of any HCV polyprotein. Said lymphoproliferative response may be measured by either a T-helper assay comprising in vitro stimulation of PMBC from patients with hepatitis C infection with varying concentrations of peptides to be tested for T-cell stimulating activity end counting the amount of radiolabelled thymidine uptake. Said lymphoproliferative response may also be measured by means of a CTL assay measuring the lytic activity of cytotoxic cells using ^{51}Cr release. Proliferation is considered positive when the stimulation index (mean cpm of antigen-stimulated cultures/mean cpm of controle cultures) is more than 1, preferably more than 2, most preferably more than 3. In order to select a T-cell stimulating epitope containing peptide, the results of these lymphoproliferative assays ere compared and immunodominant T-cell epitope containing polypeptides or peptides are selected. The results of the lymphoproliferative assays against certain peptides may also be compared between clinical non-responders and responders to interferon-α treatment. The lymphoproliferative response towards e series of synthetic, overlapping peptides representing the HCV core, E1 and E2/NS1 sequences and a recombinant NS3 protein was monitored in 32 patients with chronic HCV hepatitis as disclosed in the Examples section of the present invention.

[0029] Consequently, the present invention represents a selection of immunodominant T cell epitopes from a series of antigens covering the core region. From the examples section, it is clear that not only peptide pools 2 and 3 and peptides NS1-5* and NS1-7* but also, pools 4, 5, 6 and 9 and NS3, reacted frequently with hepatitis C patients (Table 4) while infrequent reactivity could only be observed in normal controls with the same polypeptides (Table 5). It is obvious from the data presented in Table 4 that large areas of the HCV structural region, such as pool 1 (amino acids 5-72) and pools 7 and 8 (emino acids 427-578) show little reactivity with T cells of infected patients, even with patients with a response to IFN-α treatment. Most strikingly, however, it was found that while the dominant B cell response to hepatitis C in general is located to the core aminoterminus (see also Table 3), the dominant T cell response is directed towards the core carboxyterminal region (see Table 4). In the literature, ample evidence can be found that the core carboxyterminal half contains little or no B cell-reactive epitopes. Based on the present invention, it may be desirable to yet include for instance parts of the core carboxyterminal region (spenning amino ecids 73-176) into prophylactic or therapeutic vaccine compositions.

[0030] The words "polypeptide" and "peptide" are used interchengeably throughout the specification and designate a linear series of emino acids connected one to the other by peptide bonds between the alpha-amino and carboxy groups of adjacent amino ecids. Polypeptides can be a variety of lengths, either in their natural (uncharged) forms or in forms which are salts, and either free of modifications such as glycosylation, side chain oxidation, or phosphorylation or containing these modifications. It is well understod in the art that amino acid sequences contain ecidic end basic groups, and that the particular ionization state exhibited by the peptide is dependent on the pH of the surrounding medium when the protein Is in solution, or that of the medium from which it was obtained if the proteln is in solid form. Also included in the definition are proteins modified by additional substituents attached to the amino acids side chains, such as glycosyl units, lipids, or inorganic ions such as phosphates, as well as modifications relating to chemicel conversions of the chains, such as oxidation of sulfhydryl groups. Thus, "polypeptide" or its equivalent terms is intended to include the appropriate amino acid sequence referenced, subject to those of the foregoing modifications which do

not destroy its functionality.

[0031] The polypeptides of the invention, and particularly the shorter peptides amongst them, can be prepared by classical chemical synthesis. The synthesis can be carried out in homogeneous solution or in solid phase.

[0032] For instance, the synthesis technique in homogeneous solution which can be used is the one described by Houbenweyl in the book entitled "Methode der organischen chemie" (Method of organic chemistry) edited by B. Wunsh, vol. 15-I et II. THIEME, Stuttgart 1974.

[0033] The polypeptides of the invention can also be prepared in solid phase according to the methods described by Atherton end Shepard in their book entitled "Solid phase peptide synthesis" (IRL Press, Oxford, 1989).

[0034] The polypeptides according to this invention can also be prepared by means of recombinant DNA techniques as documented below.

[0035] The polypeptides or peptides according to the present invention may, es specified above, vary in lenght. The peptides according to the invention contain at least 8 contiguous HCV amino acids. Preferred lengths of peptides are 8, 9, 10, or more (for instance 15, 20, etc.) emino acid residues.

[0036] The expression "comprised between amino acids X to Y" includes the amino acid X and the amino ecid Y.

[0037] The numbering of the HCV polyprotein used in the present invention refers to the numbering as used for the HCV-J isolate according to Kato et al., 1990. All other HCV isolates known in the ert may be aligned to this sequence to obtain the referred HCV polyprotein numbering for each individual HCV isolate. For instance, it is known that type 2 isolates can contain 4 extra codons/amino acids in their E2 sequence, while type 3 sequences have an insertion of 2 emino acids compared to type 1 sequences.

[0038] The Examples section of the present invention describes T cell epitopes in, amongst other regions of the HCV structural region: the carboxyterminal region of the core protein (aa 73-176), amino acids 192 to 383 of the E1 region, amino acids 397 and 428 end amino acids 571 to 638 of the E2 region, amino acids 1188 to 1483 of the NS3 region. Groups of peptides covering parts of the structural proteins core and E2, and covering the complete E1 protein, as well as a recombinant NS3 protein have been studied. Peptides were tested as group 1 (aa 5-80), group 2 (aa 73-140), group 3 (aa 133-200), group 4 (aa 193-260), group 5 (aa 253-332), group 6 (325-392), group 7 (aa 427-494), group 8 (aa 487-578), and group 9 (ea 571-638) as shown in Table 1. Recombinant NS3 encompassed amino acids 1188 to 1463 of the isolate IG8309, belonging to the 1b subtype group of HCV.

[0039] The T cell response to the group 3 peptides, as well as to the individual peptides NS1-7* end MS1-5* shows a statistically relevant correlation with a decrease in alanine aminotransferase (ALT) and viral RNA levels, which are generally accepted to indicate a more benign course of the diseese. A correlation between response to 'a recombinent HCV core protein' and a more benign course of the disease has been described by Botarelli et al. 1993. However, no epitopes have been mapped nor has the sequence and exact position of the recombinant core protein been described in Botarelli et al., 1993. In the present invention, a similar T cell response has been observed to the group 2 peptides (aa 73-140) both in petients responding to IFN-α and in patients non-responding to the same. On the contrary, T cell reactivity to the group 3 peptides (aa 133-200) was observed in responders to interferon-α and differed from the T cell reactivity observed to this region in non-responders to IFN-α treatment. Furthermore, after investigating the reectivity of individual peptides from groups 2 and 3, this specific response correlating with a more benign course of HCV infection, could be further mapped to specific individual peptides termed CORE 23, CORE 25, end CORE 27. Peptide CORE 19, belonging to the group 2 peptides, was also recognized by some of the responders to IFN-α treatment (see Fig. 1).

[0040] Preferentially said polypeptide of the present invention is different from RALAHGVRVLEDG spenning positions 149 to 161 of the core region of HCV.

[0041] The present invention relates to the use of a polypeptide of about 8 to about 20 amino acids for the preparation of en HCV immunogenic composition, with said polypeptide comprising or consisting of about 8 to about 20 contiguous amino acids selected from the region comprised between amino acid positions 157 to 176 of the core region of HCV: NH_2-$X_{30}X_{31}X_{32}$DGX_{33}N$X_{34}X_{35}$TGNX_{36}PGCSFSI-COOH (SEQ ID NO 51), and with said contiguous amino acids containing a T-cell stimulating epitope, and wherein said polypeptide mimics the T-cell immunological stimulation properties of the polypeptide es represented in SEQ ID NO 13, and wherein X_{30} represents V or A or L, X_{31} represents L or V or I, X_{32} represents E or G, X_{33} represents V or I, and X_{34} represents F or Y, X_{35} represents A or P, X_{36} represents L or I.

[0042] The present invention also relates to the use as described above, for the preparation of en HCV immunogenic composition, with said polypeptide comprising or consisting of about 8 to about 20 contiguous amino acids selected from the region comprised between amino acid positions 157 to 176 of the core region of HCV: VLEDGVNYATGNLPGCSFSI (SEQ ID NO 13 = peptide CORE 27) or VLEDIVNYATGNLPGCSFSI (SEQ ID NO 73).

[0043] The present invention also relates to the use. es described above, for the preparation of an HCV immunogenic composition, with said polypeptide being chosen from the following list of peptides:

NH_2-$GX_{33}NX_{34}X_{35}TGNX_{36}$-COOH (SEQ ID NO 74),
NH_2-$X_{33}NX_{34}X_{35}TGNX_{36}$-COOH (SEQ ID NO 75),
NH_2-NX_{36}PGCSFSI-COOH (SEQ ID NO 76) and
NH_2-X_{36}PGCSFSI-COOH (SEQ ID NO 77).

[0044] The present invention also relates to the use as described above, for the preparation of an HCV immunogenic composition, with said polypeptide being chosen from the following list of peptides:

GVNYATGNL (SEQ ID NO 78),
NLPGCSFSI (SEQ ID NO 80) and
LPGCSFSI (SEQ ID NO 81).

[0045] The present invention also relates to the use of a polypeptide of ebout 8 to ebout 20 amino acids for the preparation of an HCV immunogenic composition, with said polypeptide comprising or consisting of about 8 to about 20 contiguous amino acids selected from the region comprised between emino acid positions 145 to 164 of the core region of HCV:
NH_2-$GGX_{25}X_{26}X_{27}X_{28}LX_{29}HGVRX_{30}X_{31}X_{32}DGX_{33}NX_{34}$-COOH (SEQ ID NQ 52), and with said contiguous amino acids containing a T-cell stimulating epitope, and wherein said polypeptide mimics the T-celi immunological stimulation properties of the polypeptide as represented in SEQ ID NO 12, and wherein X_{25} represents A or V, X_{26} represents A or S, X_{27} represents R or A, X_{28} represents A or T or E, X_{29} represents A or E, X_{30} represents V or A or L, X_{31} represents L or V or I, X_{32} represents E or G, X_{33} represents V or I, and X_{34} represents F or Y.
[0046] The present invention also relates to the use as described above for the preparation of an HCV immunogenic composition, with said polypeptide comprising or consisting of about 8 to ebout 20 contiguous amino acids selected from the region comprised between emino acid positions 145 to 164 of the core region of HCV:

GGAARALAHGVRVLEDGVNY (SEQ ID NO 12 = peptide CORE 25) or
GGVAARALAHGVRVLEDGVNY (SEQ ID NO 116).

[0047] The present invention also contemplates the use as described above for the preparation of an HCV immunogenic composition, with said polypeptide being chosen from the following list of peptides:

NH_2-$X_{28}LX_{29}HGVRX_{30}X_{31}$-COOH (SEQ ID NO 82), NH_2-$LX_{29}HGVRX_{30}X_{31}$-COOH (SEQ ID NO 83), NH_2-$GVRX_{30}X_{31}X_{32}DGX_{33}$-COOH (SEQ ID NO 84), NH_2-$VRX_{30}X_{31}X_{32}DGX_{33}$-COOH (SEQ ID NO 85), NH_2-$RX_{30}X_{31}X_{32}DGX_{33}NX_{34}$-COOH (SEQ ID NO 86), and NH_2-$X_{30}X_{31}X_{32}DGX_{33}NX_{34}$-COOH (SEQ ID NO 87).

[0048] The present invention also relates to the use es described above for the preparation of an HCV immunogenic composition, with said polypeptide being chosen from the following list of peptides: ALAHGVRVL (SEQ ID NQ 88), LAHGVRVL (SEQ ID NQ 89), VRVLEDGV (SEQ ID NQ 90), RVLEDGV (SEQ ID NQ 91), VLEDGVNY (SEQ ID NO 92), and LEDGVNY (SEQ ID NQ 93).
[0049] The present invention also relates to the use of a polypeptide of about 8 to ebout 20 amino ecids for the preparation of an HCV immunogenic composition, with said polypeptide comprising or consisting of about 8 to about 20 contiguous amino acids selected from the region comprised between amino acid positions 133 to 152 or the core region of HCV:
NH_2-$LX_{19}X_{20}$YIP$X_{21}X_{22}GX_{23}PX_{24}GGX_{25}X_{26}X_{27}X_{28}LX_{29}$ -CQQH (SEQ ID NO 53), and with said contiguous amino

acids containing a T-cell stimulating epitope, end wherein said polypeptide mimics the T-cell immunological stimulation properties of the polypeptide as represented in SEQ ID NO 11, and wherein X_{19} represents M or I, X_{20} represents G or E, X_{21} represents L or V or I, X_{22} represents V or L, X_{23} represents A or G, X_{24} represents L, V or I, X_{25} represents A or V, X_{26} represents A or S, X_{27} represents R or A, X_{28} represents A or T or E, X_{29} represents A or E.

[0050] The present invention elso relates the use as described above for the preparation of an HCV immunogenic composition, with said polypeptide comprising or consisting of about 8 to about 20 contiguous amino acids selected from the region comprised between amino acid positions 133 to 152 of the core region of HCV:

LMGYIPLVGAPLGGAARALA (SEQ ID NO 11 = peptide CORE 23).

[0051] The present invention also relates the use as described above for the preparation of an HCV Immunogenic composition, with said polypeptide being chosen from the following list of peptides:

NH_2-$X_{19}X_{20}$YIPX$_{21}X_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 62),
NH_2-$X_{19}X_{20}$YIPX$_{21}X_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 63),
NH_2-YIPX$_{21}X_{22}GX_{23}PX_{24}$-COOH (SEQ ID NO 64),
NH_2-IPX$_{21}X_{22}GX_{23}PX_{24}$-COOH (SEQ ID NO 65),
NH_2-X$_{21}X_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 66), and
NH_2-X$_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 68)

The present invention also relates to the use as described above for the preparation of an HCV Immunogenic composition, with said polypeptide being chosen from the following list of peptides:

LMGYIPLV (SEQ ID NO 69), MGYIPLV (SEQ ID NO 70), YIPLVGAPL (SEQ ID NO 71), IPLVGAPL (SEQ ID NO 72), LVGAPLGGA (SEQ ID NO 94), and VGAPLGGA (SEQ ID NO 95).

[0052] The present invention also relates to the use of a polypeptide of about 8 to about 20 amino ecids for the preparation of an HCV immunogenic composition, with said polypeptide comprising or consisting of about 8 to about 20 contiguous amino acids selected from the region comprised between amino ecid positions 109 to 128 of the core region of HCV:
NH_2-$X_{11}X_{12}$DPRX$_{13}X_{14}$SRNX$_{15}$GX$_{16}$VIDTX$_{17}$TC -COOH (SEO ID NO 54), and with said contiguous amino ecids containing a T-cell stimulating epitope, and wherein said polypeptide mimics the T-cell immunological stimulation properties of the polypeptide es represented in SEO ID NO 9, end wherein X_{11} represents P or O, X_{12} represents N or T, X_{13} represents R or H, X_{14} represents R or K, X_{15} represents L or V or F, X_{18} represents K or R, X_{17} represents L or I.

[0053] The present invention also relates to the use as described ebove for the preparation of an HCV Immunogenic composition, with seid polypeptide comprising or consisting of about 8 to ebout 20 contiguous amino acids selected from the region comprised between emino acid positions 109 to 128 of the core region of HCV: PTDPRRRSRNLGKVIDTLTC (SEO ID NO 9 = peptide CORE 19).

[0054] The present invention elso relates to the use es described above for the preparation of an HCV immunogenic composition, with said polypeptide being chosen from the following peptides: NH_2-NX$_{15}$GX$_{16}$VIDTX$_{17}$-COOH (SEO ID NO 96), and NH_2-X$_{15}$GX$_{16}$VIDTX$_{17}$-COOH (SEQ ID NO 97).

[0055] The present invention also relates to the use as described above for the preparation of an HCV immunogenic composition, with said polypeptide being chosen from the following peptides:

NLGKVIDTL (SEQ ID NO 98), and LGKVIDTL (SEQ ID NO 117).

[0056] The present invention also relates to the use of a polypeptide of about 8 to about 20 amino acids for the preparation of an HCV immunogenic composition, with said polypeptide comprising or consisting of at least 8 to ebout 20 contiguous emino acids selected from the region comprised between amino acid positions 73 to 92 of the core

region of HCV:
NH_2-$GX_1X_2WX_3X_4PGX_5PWPLYX_6NX_7GX_8$G-COOH (SEO ID NO 99), and with said contiguous amino acids containing e T-cell stimulating epitope, and wherein said polypeptide mimics the T-cell immunological stimulation properties of the polypeptide as represented in SEO ID NO 6, and wherein X_1 represents R or K, X_2 represents A, S or T, X_3 represents A or G, X_4 represents Q, K or R, X_5 represents Y or H, X_6 represents G or A, X_7 represents E or K, and X_8 represents C, M or L.

[0057] The present invention also relates to the use as described above for the preparation of an HCV immunogenic composition, with said polypeptide comprising or consisting of a least 8 to about 20 contiguous emino acids selected from the region comprised between amino acid positions 73 to 92 of the core region of HCV:

GRTWAQPGYPWPLYGNEGCG (SEQ ID NO 6 = peptide CORE 13).

[0058] The present invention also relates to the use as described above for the preparation of an HCV immunogenic composition, with said polypeptide being selected from:

NH_2-$X_2WX_3X_4PGX_5PW$-COOH (SEQ ID NO 100) and NH_2-$WX_3X_4PGX_5PW$-COOH (SEQ ID NO 101).

[0059] The present invention also relates to the use as described above for the preparation of an HCV immunogenic composition, with said polypeptide being selected from:

TWAQPGYPW (SEQ ID NO 102), and WAQPGYPW (SEQ ID NO 103).

[0060] The present invention relates more particularly to any of the above-mentioned uses wherein said T cell stimulating epitope is a T cell helper epitope.

[0061] According to another embodiment, the present invention relates to eny of the above-mentioned uses wherein said T cell stimulating epitope is a CTL epitope.

[0062] The present invention also relates to any of the ebove-mentioned uses, wherein said polypeptide is incorporated into a prophylactic vaccine composition.

[0063] According to another embodiment, the present invention relates to any of the above-mentioned uses, wherein said polypeptide is incorporated into a therapeutic vaccine composition.

[0064] Moreover, the present invention also contemplates a polypeptide consisting of multiple repeats, combinations or mimotopes of any of the contiguous amino acid sequences selected to contain a T-cell stimulating epitopes as defined above, with said combinations comprising two or more peptides joined into a single structure and with said mimotopes having one or more amino acid variations compared to said peptides es long as said mimotope peptides are capable of providing for immunological stimulation after which the T-cells ere reactive with at least one strain of HCV.

[0065] The term "mimotopes" refers to peptides which mimic the polypeptides as defined above immunologically. Since sequence variability has been observed fro HCV, it may be desirable to vary one or more amino acids so as to better mimic the epitopes of different strains. It should be understood that such mimotopes need not be identical to any particular HCV sequence as long es the subject compounds ere capable of providing for immunological stimulation after which the T cells are reactive with at least one strain of HCV. The polypeptides as described above, may therefore be subject to insertions, deletions and conservative es well as non-conservative amino ecid subtitutions where such changes might provide for certain advantages In their use. The peptides will preferably be as short as possible while still meintaining all of their sensitivity of the larger sequence. In certain cases, it may be desirable to join two or more peptides into e single structure. The formation of such a composite may involve covalent or non-covalent linkages.

[0066] The present invention elso contemplates the uses as defined above, with said polypeptide being a recombinant polypeptide expressed by means of an expression vector comprising a nucleic acid insert encoding a polypeptide as defined above.

[0067] The present invention relates also to the use of a recombinant expression rector conprising a nucleic insert encoding a polypeptide as defined herein, for the preparation of a HCV immunogenic composition. In order to carry out the expression of the T-cell containing polypeptides of the invention in bacteria such es E. coli or in eukaryotic cells such as in S. cerevisiae, or in cultured vertebrate or invertebrate hosts such as Insect cells, Chinese Hamster Ovary

(CHO), COS1, BHK, and MDCK cells, the following steps are carried out:

- transformation of an appropriate cellular host with a recombinant vector, or by means of adenoviruses, influenza viruses, BCG, and any other live carrier systems, in which a nucleotide sequence coding for one of the polypeptides of the invention has been inserted under the control of the appropriate regulatory elements, particularly a promoter recognized by the polymereses of the cellular host or of the live carrier system and in the case of a prokaryotic host, an appropriate ribosome binding site (RBS), enabling the expression in said cellular host of said nucleotide sequence,
- culture of said transformed cellular host under conditions enabling the expression of said insert. Recombinant virus or live carrier vectors may also be directly used as live vaccines in humans.

[0068] According to a preferred embodiment, the present invention contemplates any of the uses as defined above wherein said polypeptide is operably linked to a pathogen related immunogen such as the HCV envelope proteins E1 and E2, or the HCV NS3, NS4 or NS5 immunogens, or a HCV peptide containing a B cell epitope.

[0069] The phrase "operatively linked" as used herein means that the linkage does not interfere with the ability of either of the linked groups to function as described, e.g., to function as a T or B cell determinant. Thus, operatively linking not only includes covalent linkages, but also includes linkages capable of inducing T cell function.

[0070] The phrase "pathogen related" as used herein designates a polypeptide that is capeble of inducing the T cell function that Immunoreacts with a pathogen in native form.

[0071] The defined polypeptides can be employed as such or in combination with HCV B cell epitopes, HBsAg or HBcAg perticles, HBV immunogens, HIV immunogens, HTLV immunogens HCV peptides containing preferred B cell epitopes are detailed in for instance EP-A-0 489 968 and WO 93/18054.

[0072] Methods for operatively linking individual polypeptides through an amino acid residue side chain to form an immunogenic conjugate, i.e., a branched-chain polypeptide polymer, are well known in the art. Those methods include linking through one or more types of functional groups on various side chains and result in the respective polypeptide backbones being covalently linked (coupled) but separated by at least one side chain.

[0073] Useful side chain functional groups include epsilon-amino groups, beta- or gamma-carboxyl groups, thiol (-SH) groups and aromatic rings (e.g. tyrosine and histidine). Methods for linking polypeptides using each of the ebove functional groups are described in Erlanger (1980), Aurameas et al. (1978) and U.S. Petent No. 4,493,795 to Nestor et al.. In addition, a site-directed coupling reaction; as described in Rodwell et al. (1985), can be carried out so that the biological ectivity of the polypeptides is not substantially diminished.

[0074] Furthermore, as is well known in the art, the HBcAg protein and polypeptide immunogen can be used in their native form or their functional group content may be modified by succinylation of lysine residues or reaction with cysteine-thiolactone. A sulfhydryl group may elso be incorporated into either polypeptide by reaction of amino functions with 2-iminothiolane or the N-hydroxysuccinimide ester of 3-(3-dithlopyridyl) propionete. The polypeptides can also be modified to incorporate spacer arms, such as hexamethylene diamine or other bifunctional molecules of similar size, to facilitate linking.

[0075] Any polypeptide immunogen against which antibody production is desired can be linked to the polypeptide of the present invention protein to form an immunogenic conjugate of this invention. In preferred embodiments the polypeptide immunogen is e pathogen related immunogen and the conjugate has the capacity to induce the production of antibodies that immunoreact with the pathogen when injected in an effective amount into an animal. Exemplery immunogens of particular importance are derived from bacteria such as B. pertussis, S. typose, S, Paratyphoid A and B, C, diptheriae, C. tetani, C. botulinum, C. perfringens, B. anthracis, P. pestis, P. multocida, V. cholerae, N. meningitides, N. gonorrhea, H. influenzae, T. palladium, and the like; immunogens derived from viruses such es polio virus, adenovirus, parainfluenza virus, measles, mumps, respiratory syncytical virus, influenza virus, equine encephalomyeitis virus, hog chloera virus, Newcastle virus, fowl pox virus, rabies virus, feline and canine distemper viruses, foot end mouth disease virus, human and simian immunodeficiency viruses, and the like; rickettsiae Immunogen such as epidemic and endemic typhus, and the spotted fever groups, and the like. Immunogens are well known to the prior art in numerous references such as U.S. Patent No. 3,149,036, No. 3,983,228, end No. 4,069,313; in Essential Immunology, 3rd Ed., by Roit, published by Blackwell Scientific Publications; in Fundamentals of Clinical Immunology, by Alexander and Good, published by W.B. Saunders; and in Immunology, by Bellanti, published by W.B. Saunders. Particularly preferred pathogen related immunogens are those described in United Stetes Patent No. 4,625,015, No. 4,544,500, No. 4,545,931, No. 4,663,436, No. 4,631,191, No. 4,629,783 and in Patent Cooperation Treaty International Publication No. WO87/02775 and No. WO87/02892 all of whose disclosures ere incerporated herein by reference.

[0076] The present invention relates particularly to a peptide consisting of at least 8 contiguous amino acids of the sequence of any of the following peptides, with said peptides containing e T-cell epitope:

NH_2-$X_{30}X_{31}X_{32}DGX_{33}NX_{34}X_{35}TGN$-$X_{36}PGCSFSI$-COOH (SEQ ID NO 51)
VLEDGVNYATGNLPGCSFSI (SEQ ID NO 13 = peptide CORE 27),
VLEDIVNYATGNLPGCSFSI (SEQ ID NO 73),
NH_2-$GX_{33}NX_{34}X_{35}TGN$-X_{36}-COOH (SEQ ID NO 74),
NH_2-$X_{33}NX_{34}X_{35}TGN$-X_{36}-COOH (SEQ ID NO 75),
NH_2-$NX_{36}PGCSFSI$-COOH (SEQ ID NO 76),
NH_2-$X_{36}PGCSFSI$-COOH (SEQ ID NO 77),
GVNYATGNL (SEQ ID NO 78),
NLPGCSFSI (SEQ ID NO 80), or LPGCSFSI (SEQ ID NO 81),

wherein said peptide mimics the T-cell immunological stimulation properties of the peptide represented in SEQ ID NO 13;

NH_2-$GGX_{25}X_{26}X_{27}X_{28}LX_{29}HGVRX_{30}X_{31}X_{32}DGX_{33}NX_{34}$-COOH (SEQ ID NO 52),
GGAARALAHGVRVLEDGVNY (SEQ ID NO 12 = peptide CORE 25),
GGVAARALAHGVRVLEDGVNY (SEQ ID NO 118),
NH_2-$X_{28}LX_{29}HGVRX_{30}X_{31}$-COOH (SEQ ID NO 82),
NH_2-$LX_{29}HGVRX_{30}X_{31}$-COOH (SEQ ID NO 83),
NH_2-$GVRX_{30}X_{31}X_{32}DGX_{33}$-COOH (SEQ ID NO 84),
NH_2-$VRX_{30}X_{31}X_{32}DGX_{33}$-COOH (SEQ ID NO 85),
NH_2-$RX_{30}X_{31}X_{32}DGX_{33}NX_{34}$-COOH (SEQ ID NO 86),
NH_2-$X_{30}X_{31}X_{32}DGX_{33}NX_{34}$-COOH (SEQ ID NO 87),
ALAHGVRVL (SEQ ID NO 88), LAHGVRVL (SEQ ID NO 89),
VRVLEDGV (SEQ ID NO 90), RVLEDGV (SEQ ID NO 91), VLEDGVNY (SEQ ID NO 92), or LEDGVNY (SEQ ID NO 93),

wherein said peptide mimics the T-cell immunological stimulation properties of the peptide represented in SEQ ID NO 12;

$NH_2LX_{19}X_{20}YIPX_{21}X_{22}GX_{23}PX_{24}GGX_{25}X_{26}X_{27}X_{28}LX_{29}$-COOH (SEQ ID NO 53),
LMGYIPLVGAPLGGAARALA (SEQ ID NO 11 = peptide CORE 23),
$NH_2LX_{19}X_{20}YIPX_{21}X_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 62),
NH_2-$X_{19}X_{20}YIPX_{21}X_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 63),
NH_2-$YIPX_{21}X_{22}GX_{23}PX_{24}$-COOH (SEQ ID NO 64),

NH_2-$IPX_{21}X_{22}GX_{23}PX_{24}$-COOH (SEQ ID NO 65),
NH_2-$X_{21}X_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 66),
NH_2-$X_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 68),
LMGYIPLV (SEQ ID NO 69), MGYIPLV (SEQ ID NO 70),
YIPLVGAPL (SEQ ID NO 71), IPLVGAPL (SEQ ID NO 72),
LVGAPLGGA (SEQ ID NO 94), or VGAPLGGA (SEQ ID NO 95),

wherein seid peptide mimics the T-cell immunological stimulation properties of the peptide represented in SEQ ID NO 11;

NH_2-$X_{11}X_{12}$DPR$X_{13}X_{14}$SRN$X_{15}GX_{16}$VIDTX_{17}TC -COOH (SEQ ID NO 54),
PTDPRRRSRNLGKVIDTLTC (SEQ ID NO 9 = peptide CORE 19),
NH_2-$NX_{15}GX_{16}$VIDTX_{17}-COOH (SEQ ID NO 96),
NH_2-$X_{15}GX_{16}$VIDTX_{17}-COOH (SEQ ID NO 97),
NLGKVIDTL (SEQ ID NO 98), or LGKVIDTL (SEQ ID NO 117),

wherein said peptide mimics the T-cell Immunological stimulation properties of the peptide as represented in SEQ ID NO 9;

NH_2-$GX_1X_2WX_3X_4PGX_5PWPLYX_6NX_7GX_8G$-COOH (SEQ ID NO 99),
GRTWAQPGYPWPLYGNEGCG (SEQ ID NO 6 = peptide CORE 13),
NH_2-$X_3WX_3X_4PGX_5PW$-COOH (SEQ ID NO 100),
NH_2-$WX_3X_4PGX_5PW$-COOH (SEQ ID NO 101),
TWAQPGYPW (SEQ ID NO 102), or WAQPGYPW (SEQ ID NO 103),

wherein said peptida mimics the T-cell immunological stimulation properties of the peptide as represented In SEQ ID NO 6;

wherein X_1 represents R or K, X_2 represents represents A, S or T, X_3 represents A or G, X_4 represents Q, K or R, X_5 represents Y or H, X_6 represents G or A, X_7 represents E or K, X_8 represents C, M or L, X_9 represents W or L, X_{10} represents S, N, T, D or H, X_{11} represents P or Q, X_{12} represents N or T, X_{13} represents R or H, X_{14} represents R or K, X_{15} represents L or V or F, X_{16} represents K or R, X_{17} represents L or I, X_{18} represents F or L, X_{19} represents M or I, X_{20} represents G or E, X_{21} represents L or V or I, X_{22} represents V or L, X_{23} represents A or G, X_{24} represents L, V or I, X_{25} represents A or V, X_{26} represents A or S, X_{27} represents R or A, X_{28} represents A or T or E, X_{29} represents A or E, X_{30} represents V or A or L, X_{31} represents L or V or I, X_{32} represents E or G, X_{33} represents V or I, X_{34} represents F or Y, X_{35} represents A or P, and X_{36} represents L or I.

[0077] Moreover, the present invention contemplates en imminogenic composition consisting of or comprising at least one of the polypeptides as defined above mixed with a pharmaceutically acceptable excipient.

[0078] Before administration to patients, formulants may be added to the polypeptides or peptides of the Invention. A liquid formulation is preferred. For example, these formulants may include olls, polymers, vitamins, carbohydrates, emino acids, selts, buffers, albumin, surfectants, or bulking agents. Preferably carbohydrates include sugar or sugar elcohols such as mono, di, or polysaccharides, or water soluble glucans. The saccharides or glucans can include fructose, dextrose, lactose, glucose, mannose, sorbose, xylose, maltose, sucrose, dextran, pullulan, dextrin, alpha and beta cyclodextrin, soluble starch, hydroxethyl starch end carboxymethylcellulose, or mixtures thereof. Sucrose is most preferred. "Sugar alcohol" is defined as e C4 to C8 hydrocarbon having an -OH group and includes galactitol, Inositol, mannitol, xylitol, sorbitol, glycerol, and arabitol. Mannitol is most preferred. These sugars or sugar alcohols mentioned ebove may be used individually or in combination. There is no fixed limit to amount used as long as the

sugar or sugar alcohol is soluble in the aqueous preparation. Preferably, tha sugar or sugar alcohol concentration is between 1.0 w/v% and 7.0 w/v%, more preferable between 2.0 end 6.0 w/v%. Preferably amino acids include levorotary (L) forms of carnitine, erginine, and betaine; however, other emino ecids may be added. Preferred polymers include polyvinylpyrrolidone (PVP) with en average molecular weight between 2,000 and 3,000, or polyethylene glycol (PEG) with en average molecular weight between 3,000 and 5,000. It is also preferred to use a buffer in the composition to minimize pH chenges in the solution before lyophilization or after reconstitution. Most any physiological buffer may be used, but citrate, phosphate, succinate, and glutamate buffers or mixtures thereof are preferred. Most preferred is a citrate buffer. Preferably, the concentration is from 0.01 to 0.3 molar. Surfactants that can be added to the formulation are shown in EP patent applications No. EP 0 270.799 end EP 0 268 110.

[0079] Additionally, polypeptides can ba chemically modified by covalent conjugation to a polymer to increase their circulating half-life, for example. Preferred polymers, and methods to attach them to peptides, are shown in U.S. Patent Nos. 4,766,106; 4,179,337; 4,495,285; end 4,609,546. Preferred polymers are polyoxyethylated polyols and polyethylene glycol (PEG). PEG is solubla in water at room temperature and has the general formula: $R(O\text{-}CH_2\text{-}CH_2)_nO\text{-}R$ where R can be hydrogen, or a protective group such as en alkyl or alkanol group. Preferably, the protectiva group has between 1 and 8 carbons, more preferably it is methyl. The symbol n is a positiva integer, preferably between 1 and 1,000, more preferably between 2 and 500. The PEG has a preferred average molecular weight between 1000 and 40,000, more preferably between 2000 and 20,000, most preferably between 3,000 and 12,000. Preferably, PEG has at least one hydroxy group, more preferably it is a terminal hydroxy group. It is this hydroxy group which is preferably ectivated. However, it will be understood that the type and amount of the reactive groups may be varied to achieve a covalantly conjugated PEG/polypeptide of the present invention.

[0080] Water soluble polyoxyethylated polyols ara also useful in the present invention. They include polyoxyethylated sorbitol, polyoxyethylated glucose, polyoxyethylated glycerol (POG), etc. POG is preferred. One reason is because the glycerol backbone of polyoxyethylated glycerol is the same backbona occurring naturally in, for example, animals and humans in mono-, di-, triglycerides. Therefore, this branching would not necessarily be seen as a foreign agent in the body. The POG has e preferred molecular weight in the same range as PEG. The structure for POG is shown in Knauf et al., 1988, and a discussion of POG/IL-2 conjugates is found in U.S. Patent No. 4,766,106.

[0081] Another drug delivery system for increasing circulatory half-life is the liposome. Methods of preparing liposome delivery systems are discussed in Gabizon et el., 1982; and Szoka, 1980. Other drug delivery systems are known in the art and are dascribed in, e.g. Poznansky, 1984.

[0082] After the liquid pharmaceutical composition is prepared, it is preferably lyophilized to prevent degradation and to preserve sterility. Methods for lyophilizing liquid compositions ere known to those of ordinary skill in the art. Just prior to use, the composition may be reconstituted with a sterile diluent (Ringer's solution, distilled water, or sterile saline, for example) which may include additional ingredients. Upon reconstitution, the composition is preferebly administered to subjects using those methods that are known to those skilled in the ert.

[0083] As stated above, tha polypeptides and compositions of this invention are used to treat human patients to prevent or treat eny of the above-defined disease states. The preferred route of administration is parenterally. In parenteral administration, the compositions of this Invention will be formulated in a unit dosage injectable form such as e solution, suspension or emulsion, in association with a pharmaceutically acceptable parenteral vehicle. Such vehicles are inherently nontoxic and nontherapeutic. Examples of such vehicles are saline, Ringer's solution, dextrose solution, and Hanks' solution. Nonaqueous vehicles such as fixed oils end ethyl oleate may also be used. A preferred vehicle is 5% dextrose in saline. The vehicle may contain minor amounts of additives such as substances that enhance isotonicity and chemical stability, including buffers and preservatives.

[0084] The dosage and mode of administration will depend on the individual.

[0085] Mora particularly, tha present invention contemplates a composition as defined above for use in a method of immunizing against HCV, comprising administrating a sufficient amount of at least one of the polypeptides as defined above, possibly eccompanied by pharmaceutically acceptable adjuvants, to produce an immune response.

[0086] More particularly, said Immunogenic composition is a vaccine composition. Even more particularly, said vaccina composition is e prophylactic vaccine composition. Alternatively, said vaccine composition may also be a therapeutic vaccine composition.

[0087] The prophylactic vaccine composition refers to a vaccine composition aimed for preventing HCV infection and to ba administered to normal persons who are not yet infected with HCV.

[0088] The therapeutic vaccine composition refers to a vaccine composition eimed for traatment of HCV infection and to ba administerad to patients being infected with HCV.

[0089] Tha polypeptides described in tha presant invention can ba modified with lipid (lipopeptidas, e.g. PAM_3Cys), and formulated with alum, monophosphoryl lipid A, pluronics, SAF1, Ribi, trehalose-6,6-dimycolata or other immunostimulating compounds known to those skilled in the art, as to enhance their immunogenicity.

[0090] Also, the present invention contemplates according to a preferred embodiment, a composition as defined above, with said composition comprising in addition to any of tha T cell-stimulating polypeptides as definad above, a

peptide or polypeptide containing at least one B-cell epitope of HCV, and/or a structurel HCV polypetide, and/or a non-structural HCV polypeptide.

[0091] According to a yet other preferred embodiment, the present invention contempletes a composition es defined ebove for use in a method of treatment of HCV, comprising administrating a sufficient amount of at least one of the polypeptides es defined ebove, possibly accompanied by pharmaceutically ecceptable adjuvants, to allow treatment of HCV infection. In this case the polypeptides of the present invention can be employed in the form of therapeutic vaccine, aiming at the induction of a sufficient level of T cell function for clearance of Hepatitis C virus infection.

[0092] According to yet another preferred embodiment, the present invention contemplates a composition as defined above, with said composition comprising in addition to any of the polypeptides as defined above, a peptide or polypeptide containing at least one B-cell epitope of HCV, and/or e structural HCV polypeptide, and/or a non-structurel HCV polypeptide.

[0093] According to yet enother embodiment, the present invention contemplates a composition wherein said polypeptides es defined above are mixed with HBsAg or HBcAg parıcles, HBV immunogens, HIV immunogens and/or HTLV immunogens.

Figure legends

[0094] Figure 1: Evolution of the lymphoproliferative responses and transaminase activities in HCV patient No. 632. AST depicts aspartate aminotransferase, ALT depicts elanine aminotransferase; SI: simulation index; P1 to P6 refers to the groups of peptides 1 to 6 as disclosed in Table 1.

[0095] Figure 2: Frequencies of lymphoproliferation responses to peptide pools 1-9, single peptides NS1-7*, NS1-5* and recombinant NS3 protein in healthy controls, interferon (IFN) responders and IFN non-responders.

[0096] Figure 3: represents the part of the sequence of the isolate IG8309 which has been tested, with said part extending from with Gly at position 41 to Ser at position 318 (SEQ ID NO 57).

[0097] Figure 4: represents an alignment of the HCV structurel regions.

[0098] Figure 5. Alignment of E2 region spanning amino acid positions 571 to 638.

[0099] Figure 6. Aligment of NS3 sequences spanning amino acid positions 1188 to 1465.

EXAMPLES

Example 1. Patients studied

[0100] The patients studied consisted of 19 males and 13 females, aged between 27 and 71 (mean age: 49.9 years). The diagnosis of chronic HCV hepatitis was based on e) a documented elevation of alanine aminotransferase of 2 times the upper limit of normal for at least six months; b) the presence of HCV-specific serum antibodies detected by two second generation enzyme immunoassay tests (UBI test and Innotest HCV AbII, Innogenetics, Antwerp Belgium) and c) absence of clinical, histological or serological signs of other viral, toxic, metabolic, hereditary or auto-immune hepatitis. The patients were randomized to receive either the standard treatment consisting of 3 million units Interferon α-2b (INTRON A) given thrice weekly for 24 weeks or an experimental treatment consisting of an induction phase of 6 million units Interferon α-2b thrice weekly for eight weeks, followed by a maintenance phase of titrated doses of interferon of 6 to 1 million units thrice weekly until biochemical and virological remission (alanine aminotransferase activity normal, plasma hepatitis C virus-RNA undetectable) was achieved. Patients were considered clinical responders when a normalizetion of alanine aminotransferase activity was observed on at leest two successive control visits during treatment with el least one month interval.

[0101] As controls for the specificity of the lymphoproliferative responses, 18 healthy individuals aged 25-58 years (mean 38.6), 10 males and 8 females were selected. These subjects were negative for HCV antibodies and HCV-RNA. One subject had a history of past hepatitis B virus infection and 7 had entibodies to HBsAg as a result of vaccination.

[0102] A liver biopsy was performed in ell patients prior to the Initiation of Interferon-α therapy. The histological status was defined eccording to conventional histological classification (Knodell et al., 1981).

[0103] Based on the definition of clinical responders given above, 18 subjects could be considered clinical responders to Interferon-α. The most relevant clinical, pathological and virological data of both groups are summarized in Table 2. Although the responder group contained more women and the non-responder group more men than theoretically expected, the observed imbalances were not significant (X^2-test). The duration of the disease in eech subject was estimated based on enamnestic data (surgery with multiple transfusions, intravenous drug abuse, professional exposure through needle stick accident, etc.) or patient file data displaying chronically fluctuating and elevated transaminase levels. The disease duration varied from one to 32 years. The mean diseese duration was 9.2 ± 9.2 years in responders and 6.8 ± 5.4 years in non-responders. Although the responder group conteined more subjects treated with the experimental protocol end the non-responder group more subjects treated with the standard protocol, the imbalance was

not significant X^2-test). Twenty six out of 32 patients (81%) were infected with HCV of genotype 1b. The genotypes 3a, 4a and 5a were found in 4, 1 end 1 subject, respectively. Anamnestic data allowed us to retrieve the source of infection. Blood transfusions ere the possible source of the HCV infection in 14 subjects, IV drug abuse in 3 patients and needle stick eccidents in 3 others. No source of infection could be traced back in 12 subjects. Most patients (20 out of 32) showed pathological lesions compatible with chronic active hepatitis in a mild, moderate or severe form. Seven patients displayed signs of chronic persistent hepatitis. In two subjects the biopsy showed only aspecific lesions and in two others signs of liver cirrhosis were observed.

Example 2. Analysis of the humoral immune response

[0104] INNO-LIA HCV AbII (Innogenetics, Belgium) was employed to detect antibodies to peptide epitopes from the core, NS4a+b and NS5a region. From each patient e serum sample obtained before the start of the interferon therapy was examined and sometimes, additional follow-up samples were also tested. All 32 patients studied had circulating antibodies towards HCV demonstrated by two commercially aveileble enzyme immunoassays. Using a peptide-based immunoblot assay (INNO-LIA HCV AbII) we were able to partially define the specificities of these antibodies. Sera from 31 patients were examined at least once with this assay and in 20 subjects the assay was applied on two sera taken with an interval of 4 (Patient 635) to 124 weeks (Patient 606). Table 3 shows the results of this survey. Apart from the reactivity pattern with the antigens employed (4 individually spotted core peptides, a mixture of NS4 peptides defining a fifth line and a selection of NS5 peptides creating a sixth line), Table 3 also shows the HCV genotype and the moment at which the serum was taken with respect to the start of the interferon therepy. The data clearly indicate that the antibody recognition pattem of an individual patient hardly changes over time. The only differences observed in the 20 paired samples were single step alterations in the intensity of the reactions. As well in responders as in non-responders to interferon we observed the same hierarchy in the serological reaction pattems. When Indeterminate or weak reactions are not taken into consideration, the following hierarchy appears: Core2 > NS4 > NS5 > Corel > Core4 > Core3.

Example 3. Detection of HCV RNA and HCV genotyping

[0105] Reverse transcription and PCR was performed es described previously (Stuyver et al, 1993). PCR products were further processed for genotyping by means of the Inno-LiPA genotyping assay (Stuyver et al., 1993). The results of the genotyping assays are included in Table 3.

Example 4. Analysis of the cellular Immune response

4.1. Synthesis of HCV antigens

[0106] Nine groups of peptides (pools) corresponding to Core, E1 and E2/NS1 sequences, two single peptides not included in these pools corresponding to E2/NS1, and e recombinant protein representing the central part of NS3-HCV genotype 1b, were used for in vitro stimulation of PBMC. Eech group pooled 4-6 different 20-mer peptides which overlapped 8 emino ecids. Groups 1, 2 and 3 included mainly core peptides with amino ecid positions 5-80, 73-140 and 133-200, respectively (Table 1). Groups 4, 5 and 6 predominantly encompassed E1 peptides with amino acid positions 193-260, 253-332 end 325-392, respectively. Groups 7, 8 and 9 comprised E2/MS1 peptides with amino acid positions 427-494, 487-578 and 571-638, respectively. The two additional single peptides (MS1-7*, end NS1-5*) covered amino acids from 397 to 428 of the E2 sequence (Table 1). A fusion protein containing the NS3 sequence wes expressed in E. coli and covered HCV amino acids 1188 to 1463 of the Belgian isolate IG8309.

[0107] Peptides were dissolved in the buffers shown in Table 1 and added to the cultures at a final concentration of 10 µg/ml. At this peptide concentretion, the concentration of dissolving buffers in the cell cultures was not toxic or inhibitory. Preliminary experiments were performed to ascertain this. NS3 protein was used at a final concentration of 1.5 µg/ml. Tetanus toxoid (WHO, Copenhagen, Denmark), used as a positive control antigen, was added to the culture media at a final concentration of 10 µg/ml.

[0108] All the peptides were synthesized on either PepSyn K resin (Millipore) functionalized with the acid labile linker 4-(a-Fmoc-emino-2',4'-dimethoxybenzyl) phenoxyacetic ecid, or TentaGel S-RAM resin (Repp Polymere) functionalized with the same linker which yields peptide amides upon cleavage. t-Butyl-besed side chain protection end Fmoc-a-amino protected amino acid derivatives were used. The guanidino group of arginine was 2,2,5,7,8-pentamethylchroman-8-sulfonyl-protected. The imidazole group of histidine was protected with either t-Boc or trityl and the sulfhydryl group of cysteine was protected with a trityl group. Couplings were carried out using preformed O-pentafluorophenyl esters except in the case of erginine where TBTU (O-(1H-benzotriazol-1-yl)-N,N,N',N',-tetramethyluronium tetrefluoroborate.; Novabiochem) was used as the ectivating agent in the presence of 2 equivalents of the base N-methylmorpholine and 1 equivalent of 1-hydroxybenzotriazole. Occasionally, glutamine, asparagine, end tryptophan were also

coupled using TBTU activation. In these cases, the trityl-protected derivatives of glutamine and asparagine (Millipore), and the t-Boc-protected derivative of tryptophan (Novabiochem) were used. All syntheses were carried out on a Milligen 9050 PepSynthesizer (Millipore) using continuous flow procedures. Following cleavage of the peptides with trifluoroacetic ecid in the presence of appropriate scavengers and precipitation with diethylether, all peptides were enalyzed by C_{18}-reverse phase chromatography.

[0109] HCV amino acid sequences corresponding to the virel nucleocapsid (core) and E1 proteins were based on the HC-J1 sequence described by Okamoto *et al.* (1990) Japan. J. Exp. Med. (1990) 60:167-177). HCV sequences starting et emino acid residue Gly_{451} were taken from the sequences reported by Choo *et el.* (1991) Proc. Natl. Acad. Sci. USA (1991) 88:2451-2455. Most peptide sequences were chosen such that the peptides would overlap each other by 8 amino acid residues.

4.2. T cell proliferation assays

[0110] The medium used for all cell cultures consisted of RPMI 1640 supplemented with 25 mM HEPES, 2 mM L-glutamine, 50 U/ml penicillin and 50 µg/ml streptomycin (all from Gibco Europe, Gent, Belgium), 5×10^{-5} M 2-mercaptoethanol (Sigma, St. Louis, Mo.) and 10% heat-inactivated pooled human AB serum. This AB serum was obtained from healthy blood donors with blood group AB^+ and was only used when antibodies to HCV end HCV-RNA were ebsent. This "complemented" RPMI 1640 medium will hereafter be designated "complete medium".

[0111] PBMC were isolated from heparinized venous blood by isopycnic density centrifugation on Ficoll Hypaque (Lymphoprep, Nyegaard, Denmark) and suspended in complete medium. $4x10^5$ PBMC in 200 µl of complete medium were cultured in 96 well roundbottomed microplates (Falcon Plastics) in the absence (unstimulated controls) or presence of varying concentrations of entigens for 5 days at 37°C in en atmosphere of 5% CO_2 in air. 0.5 µCi (^{3}H)-thymidine was then added to each well and 16 to 20 h later the cultures were harvested onto glass fiber filters using e multichannel cell harvester (PHD, Cambridge, MA) to measure the incorporation of (^{3}H)-thymidine by liquid scintillation counting in an LKB-Wallac 8100 counter (LKB, Bromma, Sweden). Results are expressed as stimulation index (SI; mean cpm of antigen-stimulated cultures/mean cpm of control cultures). Proliferetion was considered positive when stimulation index was >3. In some figures the results ere expressed as cpm (mean cpm of entigen-stimulated cultures - mean cpm of control cultures). Standard deviations of the mean cpm of triplicate cultures were consistently below 10%.

[0112] The occurrence of *in vivo* primed HCV-specific memory T, lymphocytes was exemined using a lymphoproliferation assay. PBMC from 32 patients with chronic HCV were stimulated *in vitro* with pools of 4 to 6 partially overlapping, synthetic peptides representing the core, E1 and E2/NS1 regions of HCV type 1a, with 2 overlapping, single peptides from the amino-terminus of HCV type 1a and with a recombinant fusion protein containing the NS3 sequence of HCV type 1b. In all but 2 patients (#610 and #636) at least 2 and up to 11 (#633) assays were performed. In patient # 632 for example lymphoproliferation was examined on 8 different occasions between week 4 and 54 following the start (week 0) of the Interferon therapy. Figure 1 shows the results of these assays in correlation with the biochemical (ALT/AST) response to therapy. Four weeks after the start of Intron-A (Schering Plough) a normalization of the transaminase levels was observed. PBMC's from the patient consistently end vigorously proliferate upon stimulation with peptide pools 2 end 3. The responses to the other antigen preparations were less vigorous and less reproducible, suggesting that the number of memory cells recognizing these epitopes is lower. Antigens that did not induce a proliferative response with e stimulation index (SI) 3 et any time are not represented in the graph.

[0113] To anelyze end summarize the results of 135 assays performed in the 32 HCV patients, we have chosen to consider the response of an individual patient to a particular entigen preparation (peptide pools 1 to 9, NS1-5*, NS1-7* or NS3 protein) as significant when it induces SI's 3 in at least half of the assays performed. The results shown in Table 4 have been obtained using this scoring method. The Table shows the entigen recognition pattern of chronic HCV patients towards the 12 antigen preparations standardly used. Apart from the individual patient number and the number of assays performed with PBMC's from each subject, Table 4 also shows the time frame wherein these assays were executed. The start of the Interferon therapy serves as the reference point, week 0. None of the patients responded to all the entigens. PBMC's from 13 of 18 (72%) clinical responders and 12 of 14 (85%) non-responders proliferated in response to at least one antigen preparation. All but one antigen preparetion, peptide pool 8, induced a proliferative response in at least one subject. The most frequent responses were to peptide pools 2 end 3. Whereas both interferon-responders and non-responders proliferated equally well to peptide pool 2 (56% and 57%, respectively), non-responders reected less well to peptide pool 3 (29% or 4 of 14) than responders (44% or 8 of 18). Similer imbalances were observed for the reactions to peptide pools 5 and 9, that were more frequently recognized by non-responders (43% and 43%, respectively) then by responders (17% and 11%, respectively). Clinical non-responders to interferon therapy also reacted more frequently (57% or 8 of 14) upon stimuletion with the NS3 protein than responders (24% or 4 of 17). However, none of these differences in proliferative response rates to peptide pools 3, 5 and 9 or to NS3 protein reached statistical significance ($p<0.05$ in ^{2}-test). A striking end significant difference ($p=0.01$ in ^{2}-test) was observed for the response rate of responders and non-responders to peptides NS1-5* and NS1-7*. Indeed, 8 of 17 responders recog-

nized one or both peptides while none of the non-responders did so. A summary of the results of all these proliferation assays is provided in Figure 2, in which the response rates of the HCV patients as well as 1B healthy control subjects towards the 12 antigen preperations. Indeed, to establish the relevance of the proliferative responses observed in HCV patients, PBMC's from 18 healthy control subjects were stimulated with the same antigen preparations. Overall, 27 assays were performed: a single assay in 10 subjects, two in 7 volunteers and 3 in one individual. In 12 control subjects none of the entigens induced a proliferative response. In 6 subjects one or more antigens induced a proliferative response with an SI 3 in a unique assay or in at least half of the assays performed. Table 5 shows the antigens that induced the proliferation in these subjects. Although Figure 2 suggests that proliferative responses occur more frequently in HCV patients than in healthy controls, these differences do not always reach statistical significance ($p< 0.05$). Peptide pools 2 and 3 end the NS3 protein clearly ($p<0.05$) induce'more frequent proliferative responses in the whole group of HCV patients than in healthy controls. Most of these differences are also significant when interferon responders and non-responders are each compared to the healthy control group. Only for the proliferative response to NS3 of interferon responders this is no longer valid. Although the frequency of proliferative response to peptide pool 5 In healthy controls and HCV patients were not significantly different, they turned out to be so ($p<0.03$) when only the non-responders were compared to the control subjects. All other differences did not reach the $p<0.05$ level.

Example 5. Fine specificity of the recognition of the HCV core region by PBMC from clinical responders: T cell epitope localization in the core carboxyterminal region

[0114] Since peptide pools 2 and 3 elicited proliferative responses in a large fraction of HCV patients, we have examined which peptides from these pools were inducing these responses. The stimulatory capacity of single peptides on PBMC's from healthy control subjects was tested as well. Twenty-three proliferation assays were performed with PBMC's from 17 control subjects. Peptides core C17, core C21 and core C31 were recognized by 2, 1 and 1 subject or 12%, 6% and 6% of subjects, respectively. PBMC's were prepared from 11 HCV patients that responded to interferon therapy. Eight subjects had displayed a proliferative response to either one or both peptide pools 2 and 3, whereas 3 patients had not. Nineteen assays were performed. The scoring system for positive reactions was as described in example 4. Table 6 summarizes the results of these 19 assays and demonstrates the consistency of the assay results. Indeed, PBMC's from the patients that had not reacted to the peptide pools did not proliferete upon stimulation with any of the individuel peptides. The PBMC's from the patients that had displayed a proliferative response before, also reacted upon stimulation with one or several peptides from these pools. At least one and up to five of these peptides were recognized by these patients. The most immunogenic region of the HCV core sequence seems to be located between amino acids 109 end 176. Peptides C27 (AA 157-176), recognized by 6 of the 8 proliferative responders, turns out to be the most immunodominant one, followed by C25 which is recognized by 5 patients, and C23 end C19 which are recognized by 3 subjects.

Example 6

[0115] The fine specificity of the lymphoproliferative responses was tested again with new samples, the majority of which was obtained from other patients than those analyzed in example 5. Five patients (two αIFN responders and three αIFN non-responders) and 16 normal controls were examined. Table 7 shows the results of the assays performed in chronic hepatitis C patients. The highest LPR observed in both αIFN responders tested was towards aa positions : 73-92 (C13); 109-12B (C19); 121-140 (C21); 145-164 (C25); 157-176 (C27). Only aa residues 121-140 (C21) and 133-152 (C23) elicited a high PLR in two αIFN non-responders. Therefore, the use of peptides C13, C19, C25 and/or C27 in prophylactic or therapeutic vaccine compositions may be particularly advantageous.

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TABLE 1
Synthetic peptides used as antigens in the lymphoproliferative assays.

HCV REGION	POOL	PEPTIDE NAME	AMINO ACID (AA) SEQUENCE	AA POSITION	SEQ ID NO	SOLVENT
CORE	1	CORE 2	PKPQRKTKRNTNRRP	5-19	1	A
		CORE 3	RNTNRRPQDVKFPGGGQIVG	13-32	2	A
		CORE 5	PGGGQIVGGVYLLPRRGPRL	25-44	3	B
		CORE 9	TRKTSERSQPRGRRQPIPKV	49-68	4	A
		CORE 11	RRQPIPKVRRPEGRTWAQPG	61-80	5	A
	2	CORE 13	GRTWAQPGYPWPLYGNEGCG	73-92	6	B
		CORE 15	LYGNEGCGWAGWLLSPRGSR	85-104	7	C
		CORE 17	LLSPRGSRPSWGPTDPRRRS	99-116	8	A
		CORE 19	PTDPRRRSRNLGKVIDTLTC	109-128	9	A
		CORE 21	KVIDTLTCGFADLMGYIPLV	121-140	10	D
	3	CORE 23	LMGYIPLVGAPLGGAARALA	133-152	11	A
		CORE 25	GGAARALAHGVRVLEDGVNY	145-164	12	A
		CORE 27	VLEDGVNYATGNLPGCSFSI	157-176	13	B
		CORE 29	LPGCSFSIFLLALLSCLTVP	169-188	14	O
		CORE 31	LLSCLTVPASAYQVRNSTGL	181-200	15	C
E1	4	E1-33	QVRNSTGLYHVTNDCPNSSI	193-212	16	O
		E1-35	NDCPNSSIVYEAHDAILHTP	205-224	17	C
		E1-37	HDAILHTPGCVPCVREGNVS	217-236	18	A
		E1-39	CVREGNVSRCWVAMTPTVAT	229-248	19	H
		E1-41	AMTPTVATRDGKLPPATQLRR	241-260	20	A
	5	E1-43	LPATQLRRHIDLLVGSATLC	253-272	21	H
		E1-45	LVGSATLCSALYVGDLCGSV	265-284	22	E
		E1-49	QLFTPSPRRHWTTQGCNCSI	289-308	23	H
		E1-51	TQGCNCSIYPGHITGHRMAW	301-320	24	E
		E1-53	ITGHRMAWDMMMNWSPTAAL	313-332	25	H
*	6	E1-55	NWSPTAALVMAQLLRIPQAI	325-344	26	H
*		E1-57	LLRIPQAILDMIAGAHWGVL	337-356	27	H
+/+		E1-59	AGAHWGVLAGIAYFSMVGNW	349-368	28	E
		E1-63	VVLLLFAGVDAETIVSGGQA	373-392	29	E
E2/NS1	7	NS1-3*	LNCNESLNTGWVLAGLFYQH	427-446	30	C
		NS1-1*	AGLFYQHKFNSSGCPERLAS	439-458	31	B
		NS1-1	GCPERLASCRPLTDFDQGWG	451-470	32	B
		NS1-3	TDFDQGWGPISYANGSGPDQ	463-482	33	A
		NS1-5	ANGSGPDQRPYCWHYPPKPC	475-494	34	A
	8	NS1-7	WHYPPKPCGIVPAKSVCGPV	487-506	35	B
		NS1-9	AKSVCGPVYCFTPSPVVVGT	499-518	36	O
		NS1-11	PSPVVVGTTDRSGAPTYSWG	511-530	37	C
		NS1-13	GAPTYSWGENDTDVFVLNNT	523-542	38	E
		NS1-17	GNWFGCTWMNSTGFTKVCGA	547-566	39	O
		NS1-19	GFTKVCGAPPVCIGGAGNNT	559-578	40	A
	9	NS1-21	IGGAGNNTLHCPTDCFRKHP	571-590	41	A
		NS1-23	TDCFRKHPDATYSRCGSGPW	583-602	42	A
		NS1-25	SRCGSGPWITPRCLVDYPYR	595-614	43	B
		NS1-27	CLVDYPYRLWHYPCTINYTI	607-626	44	C
		NS1-29	PCTINYTIFKIRMYVGGVER	619-638	45	A
		NS1-7'	SGLVSLPTPGAKQNIQLNT	397-416	46	C
		NS1-5'	QNIQLNTNGSWHINSTALN	409-428	47	C

Solvents used:
Solvent A: 0.1% trifluoroacetic acid; Solvent B: 0.1% trifluoroacetic acid, 25% acetonitrile; Solvent C: 0.1% trifluoroacetic acid, 30% acetonitrile; Solvent D: 0.1% trifluoroacetic acid, 50% acetonitrile; Solvent E: 0.005 ammonia buffer; Solvent O: 50% dimethyl sulfoxide; Solvent H: 0.1% trifluoroacetic acid, 40% acetonitrile.

Table 2. General data from HCV patients.

				CLINICAL	RESPONDERS			
Patient	Gender	Age	AP Diagnosis	Source	Duration (Years)	Genotype	IFN Scheme	ALT before therapy
604	F	30	CAH: mod	IVDA	10	1b	2	150
607	M	39	CPH	Unknown	2	1b	1	182
608	M	61	CAH: mild	Transfusion	7	3a	1	196
610	F	27	Non spec	Unknown	2	1b	2	219
614	M	56	CAH: mild	Transfusion	10	1b	2	425
615	M	71	CAH: mod	Unknown	2	1b	1	201
616	F	52	Non spec	Transfusion	5	1b	1	152
618	F	37	CPH	Needle stick	5	1b	2	60
621	M	48	CAH: mod	Unknown	8	1b	1	63
624	M	31	CPH	Needle stick	15	1b	2	158
626	F	34	CAH: sev	Transfusion	6	3a	2	168
630	M	30	CPH	Needle stick	5	1b	2	9
632	M	57	CPH	Unknown	1	4a or 5a	2	359
633	F	30	CAH: mod	Transfusion	2	1b	2	292
634	F	67	CAH: mod	Unknown	32	1b	2	481
635	F	47	prob cirrh	Transfusion	14	1b	2	100
636	F	54	CAH: mod	Unknown	7	5a	1	90
639	F	62	CAH	Transfusion	32	1b	1	79

				CLINICAL	NON-RESPONDERS			
Patient	Gender	Age	AP Diagnosis	Source	Duration (Years)	Genotype	IFN Scheme	ALT before therapy
601	M	32	CAH: mod	Transfusion	3	1b	2	141
602	M	66	CAH: mod	Transfusion	3	1b	1	349
603	M	45	CAH: sev	Transfusion	17	1b	2	157
606	F	53	CAH: mod	Unknown	2	1b	1	299
611	M	51	CPH	Transfusion	7	1b	1	195
613	F	38	CAH: mod	IVDA	17	3a	1	178

CAH= CHRONIC ACTIVE HEPATITIS. CPH= CHRONIC PERSISTENT HEPATITIS. CIRRH= CIRRHOSIS. NON SPEC= NOT DONE OR NOT SPECIFIC ABNORMALITIES

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Table 2 continued. General data from HCV patients.

617	M	71	CAH: sev	Transfusion	3	1b	1	447
620	M	67	CAH: mod	Unknown	2	1b	1	138
622	M	40	CAH: sev	Transfusion	11	1b	1	291
625	M	70	CAH: mod	Unknown	1	1b	1	134
627	M	44	CAH: mod	IVDA	8	3a	1	254
629	F	61	Cirrh	Transfusion	11	1b	1	179
631	M	69	CPH	Unknown	5	1b	2	358
637	F	59	Cirrh	Unknown	5	1b	2	118

CAH= CHRONIC ACTIVE HEPATITIS. CPH= CHRONIC PERSISTENT HEPATITIS. CIRRH= CIRRHOSIS. NON SPEC= NOT DONE OR NOT SPECIFIC ABNORMALITIES

Table 3. Antibody reactivities to 6 HCV antigens of the Line Immuno-Assay in 32 chronic HCV patients.

CLINICAL		RESPONDERS						
Patient	Weeks	Genotype	NS4	NS5	C1	C2	C3	C4
604	- 6	1b	3	3	2	2	-	-
	90		3	3	3	3	-	2
607	- 11	1b	2	3	2	-	-	-
	84		3	3	3	-	-	-
608	- 6	3a	-	3	-	-	-	-
610	- 6	1b	3	-	2	3	-	-
614	30	1b	3	3	2	2	-	-
	60		2	3	3	3	-	-
615	- 2	1b	3	-	-	2	-	-
616	- 6	1b	3	-	2	3	2	2
618	- 6	1b	-	-	-	3	-	-
	54		-	-	-	2	-	-
621	- 3	1b	3	3	2	-	-	-
	30		3	3	2	-	-	-
624	- 5	1b	3	3	2	2	-	-
	20		3	3	2	3	2	2
626.	2	3a	-	2	2	3	-	-
	20		2	2	3	3	-	2
630	- 12	1b	3	-	2	2	-	-
	8		3	-	2	2	-	-
632	- 6	4a or 5a	-	3	2	3	2	2
	8		-	3	2	3	2	2
633	- 6	1b	3	3	-	2	-	2

"-" denotes negative, indeterminate or weak reactions. 2, moderate reaction. 3, strong reaction.

Table 4. T-cell recognition of 12 HCV antigens in 32 chronic hepatitis C patients under alpha-interferon therapy.

	CLINICAL	RESPONDERS												
Patient	Genotype	N°. Assays	Time of assays	P1	P2	P3	P4	P5	P6	P7	P8	P9	NS1-7*	NS1-5*	NS3
604	1b	2	w90-108		+	+	+	+	+			+	+	+	+
607	1b	2	w84-120		+			+				+	ND	ND	ND
608	3a	2	w90-108		+	+									
610	1b	1	w84												
614	1b	4	w60-108											+	
615	1b	2	w66-84	+	+	+	+	+							+
616	1b	3	w78-108											+	
618	1b	4	w54-84	+	+										+
621	1b	4	w30-60			+							+	+	
624	1b	9	w20-90												
626	3a	9	w16-60		+	+							+		
630	1b	6	w8-75												
632	4a or 5a	8	w4-54		+	+									
633	1b	11	w0-48												
634	1b	3	w0-24		+									+	+
635	1b	7	w-6-54												
636	5a	1	w24		+	+								+	
639	1b	4	w-3-19	+	+	+							+	+	

	CLINICAL	NON-RESPONDERS												
Patient	Genotype	N°. Assays	Time of assays	P1	P2	P3	P4	P5	P6	P7	P8	P9	NS1-7*	NS1-5*	NS3
601	1b	4	w90-140		+			+	+			+			+
602	1b	2	w96-108	+	+	+	+					+			+
603	1b	2	w78-93		+	+	+	+							+
606	1b	3	w84-96		+			+							+
611	1b	2	w66-84	+	+			+							
613	3a	8	w60-96												+
617	1b	5	w60-108												
620	1b	3	w42-66									+			+
622	1b	3	w30-54					+							+
625	1b	4	w20-66		+	+						+			
627	3a	3	w16-24		+							+			
629	1b	2	w20-48	+	+		+	+		+		+			+
631	1b	5	w4-w16												
637	1b	7	w-6-16			+									

P1-3 corresponds to Core, P4-6 represents E1. P7-9 comprises E2/NS1. (+) denotes lymphoproliferative response. ND- Not done.

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Table 5. Antigens recognized by 6 control subjects displaying significant * lymphoproliferation responses.

SUBJECTS	N° ASSAYS	P1	P2	P3	P4	P5	P6	P7	P8	P9	NS1-7*	NS1-5*	NS3
CAE	3										+		
IDS	1		+										+
LCE	1											+	
MVH	1		+		+	+				+		+	
PDG	2				+								
RDB	2		+										

* A response is considered significant when a S.I. equal or greater than 3 in a single peptide assay or in at least half of the assays performed.

Table 6. The lymphoproliferative responses to peptide pools are consistent with lymphoproliferative responses to single peptides fr.

		PEPTIDE	POOLS					SINGLE			PEPTIDES				
								P2					P3		
	Patient	N° assays	Pool 2	Pool 3	N° assays	C13	C15	C17	C19	C21	C23	C25	C27	C29	C31
	604	2	+	+	1	-	-	-	-	-	+	-	-	-	-
	615	2	+	+	1	-	-	-	-	-	+	-	+	-	-
LPR TO	618	4	+	-	1	-	-	-	-	-	-	+	+	-	-
POOLS	621	4	-	+	1	-	-	-	-	-	-	+	+	-	-
2	626	9	+	+	5	-	-	-	-	-	-	+	+	-	-
AND/OR	632	8	+	+	4	-	-	-	+	+	+	+	+	-	-
3	634	2	+	-	1	-	-	-	+	-	-	-	+	-	-
	639	4	+	+	2	-	-	-	+	-	-	+	+	-	+
NO LPR	614	3	-	-	1	-	-	-	-	-	-	-	-	-	-
TO POOLS	616	3	-	-	1	-	-	-	-	-	-	-	-	-	-
2 AND 3	633	1	-	-	1	-	-	-	-	-	-	-	-	-	-

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Table 7.

Fine specificity of T-cell recognition of P2 and P3 Core individual peptides.

Patient N°	Clinical response to αIFN[a]	Week[b]	Blank[c]	TT[d]	P2 peptides C13[e]	C15	C17	C19	C21	C23	C25	C27	P3 peptides C29	C31
626	R	14	750	14.5	4.4	-	-	-	3.3	-	6	8.2	-	-
636	R	28	1032	3.6	6.3	-	-	7.1	-	-	9.7	5.8	-	-
620	NR	20	5047	4.1	ND[f]	ND	ND	ND	ND	4.1	-	-	-	-
627	NR	54	928	19.1	-	-	-	-	3.6	-	-	-	-	-
637	NR	45	2370	4.2	-	-	-	-	-	-	-	-	-	-

[a] R: responder; NR: Not responder.
[b] Time points of αIFN therapy on which LPA were performed.
[c] Values express cpm.
[d] TT: Tetanus toxoid. Values denote SI.
[e] C13-C21 and C23-C31 are the individual peptides of P2 and P3 Core peptide pools. Only SI equal or greater than 3 are shown.
[f] ND: Not done.

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SEQUENCE LISTING

[0150]

(1) GENERAL INFORMATION:

(i) APPLICANT:

(A) NAME: Innogenetics s.a.
(B) STREET: Industriepark Zwijnaarde 7, box 4
(C) CITY: Ghent
(B) COUNTRY: Belgium
(F) POSTAL CODE (ZIP): B-9052
(G) TELEPHONE: 00 32 9 241 07 11
(H) TELEFAX: 00 32 9 241 07 99

(ii) TITLE OF INVENTION: Immunodominant human T cell epitopes of Hepatitis C virus structural proteins, prophylactic and therapeutic compositions containing the same

(iii) NUMBER OF SEQUENCES: 166

(iv) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PetentIn Release #1.0, Version #1.25 (EPO)

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15 amino acids
(B) TYPE: emino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

```
Pro Lys Pro Gln Arg Lys Thr Lys Arg Asn Thr Asn Arg Arg Pro
1               5                  10                  15
```

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

```
Arg Asn Thr Asn Arg Arg Pro Gln Asp Val Lys Phe Pro Gly Gly Gly
1               5                  10                  15

Gln Ile Val Gly
            20
```

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

```
Pro Gly Gly Gly Gln Ile Val Gly Gly Val Tyr Leu Leu Pro Arg Arg
1               5                  10                  15

Gly Pro Arg Leu
            20
```

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS;

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

```
Thr Arg Lys Thr Ser Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro
1               5                  10                  15

Ile Pro Lys Val
            20
```

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

```
Arg Arg Gln Pro Ile Pro Lys Val Arg Arg Pro Glu Gly Arg Thr Trp
1               5                  10                  15

Ala Gln Pro Gly
            20
```

(2) INFORMATION FOR SEO ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEOUENCE DESCRIPTION: SEO ID NO: 6:

```
Gly Arg Thr Trp Ala Gln Pro Gly Tyr Pro Trp Pro Leu Tyr Gly Asn
1               5                  10                  15

Glu Gly Cys Gly
            20
```

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRAMDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEO ID NO: 7:

```
Leu Tyr Gly Asn Glu Gly Cys Gly Trp Ala Gly Trp Leu Leu Ser Pro
1               5                  10                  15

Arg Gly Ser Arg
            20
```

(2) INFORMATION FOR SEO ID NO: 8:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEOUENCE DESCRIPTION: SEO ID NO: 8:

```
Leu Leu Ser Pro Arg Gly Ser Arg Pro Ser Trp Gly Pro Thr Asp Pro
1               5                  10                  15

Arg Arg Arg Ser
            20
```

(2) INFORMATION FOR SEO ID NO: 9:

(i) SEOUENCE CHARACTERISTICS;

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEO ID NO: 9:

```
Pro Thr Asp Pro Arg Arg Arg Ser Arg Asn Leu Gly Lys Val Ile Asp
1               5                  10                  15

Thr Leu Thr Cys
            20
```

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEOUENCE DESCRIPTION: SEO ID NO: 10:

```
Lys Val Ile Asp Thr Leu Thr Cys Gly Phe Ala Asp Leu Met Gly Tyr
1               5                  10                  15

Ile Pro Leu Val
            20
```

(2) INFORMATION FOR SEO ID NO: 11:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEOUENCE DESCRIPTION: SEO ID NO: 11:

```
Leu Met Gly Tyr Ile Pro Leu Val Gly Ala Pro Leu Gly Gly Ala Ala
1               5                  10                  15

Arg Ala Leu Ala
            20
```

(2) INFORMATION FOR.SEO ID NO: 12:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEOUENCE DESCRIPTION: SEQ ID NO: 12:

```
Gly Gly Ala Ala Arg Ala Leu Ala His Gly Val Arg Val Leu Glu Asp
1               5                  10                  15

Gly Val Asn Tyr
            20
```

(2) INFORMATION FOR SEO ID NO: 13:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEOUENCE DESCRIPTION: SEO ID NO: 13:

```
Val Leu Glu Asp Gly Val Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys
1               5                  10                  15

Ser Phe Ser Ile
            20
```

(2) INFORMATION FOR SEO ID NO: 14:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linaar

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

```
Leu Pro Gly Cys Ser Phe Ser Ile Phe Leu Leu Ala Leu Leu Ser Cys
1               5                  10                  15

Leu Thr Val Pro
            20
```

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

```
Leu Leu Ser Cys Leu Thr Val Pro Ala Ser Ala Tyr Gln Val Arg Asn
1               5                  10                  15

Ser Thr Gly Leu
            20
```

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

```
Gln Val Arg Asn Ser Thr Gly Leu Tyr His Val Thr Asn Asp Cys Pro
1               5                  10                  15

Asn Ser Ser Ile
            20
```

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEOUENCE OESCRIPTION: SEQ IO NO: 17:

```
Asn Asp Cys Pro Asn Ser Ser Ile Val Tyr Glu Ala His Asp Ala Ile
1               5                  10                  15

Leu His Thr Pro
            20
```

(2) INFORMATION FOR SEO IO NO: 18:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANOEDNESS: single
(O) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptida

(xi) SEOUENCE OESCRIPTION: SEO IO NO: 18:

```
His Asp Ala Ile Leu His Thr Pro Gly Cys Val Pro Cys Val Arg Glu
1               5                  10                  1S

Gly Asn Val Ser
            20
```

(2) INFORMATION FOR SEO IO NO: 19:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANOEONESS: single
(O) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE OESCRIPTION: SEO IO NO: 19:

```
Cys Val Arg Glu Gly Asn Vsl Ser Arg Cys Trp Val Ala Met Thr Pro
1               5                  10                  15

Thr Val Ala Thr
            20
```

(2) INFORMATION FOR SEQ IO NO: 20:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANOEONESS: single
(O) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

```
Ala Met Thr Pro Thr Val Ala Thr Arg Asp Gly Lys Leu Pro Pro Ala
1               5                  10                  15

Thr Gln Leu Arg Arg
            20
```

(2) INFORMATION FOR SEQ ID NO: 21:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

```
Leu Pro Ala Thr Gln Leu Arg Arg His Ile Asp Leu Leu Val Gly Ser
1               5                  10                  15

Ala Thr Leu Cys
            20
```

(2) INFORMATION FOR SEQ ID NO: 22:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

```
Leu Val Gly Ser Ala Thr Leu Cys Ser Ala Leu Tyr Val Gly Asp Leu
1               5                  10                  15

Cys Gly Ser Val
            20
```

(2) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION; SEQ ID NO: 23:

```
Gln Leu Phe Thr Phe Ser Pro Arg Arg His Trp Thr Thr Gln Gly Cys
1               5                  10                  15

Asn Cys Ser Ile
            20
```

(2) INFORMATION FOR SEQ ID NO: 24:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

```
Thr Gln Gly Cys Asn Cys Ser Ile Tyr Pro Gly His Ile Thr Gly His
1               5                  10                  15

Arg Met Ala Trp
            20
```

(2) INFORMATION FOR SEQ ID NO: 25:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

```
Ile Thr Gly His Arg Met Ala Trp Asp Met Met Met Asn Trp Ser Pro
1               5                  10                  15

Thr Ala Ala Leu
            20
```

(2) INFORMATION FOR SEQ ID NO: 26:

(i) SEQUENCE CHARACTERISTICS;

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS: single
(D) TQPQLQGY: linear

(ii) MQLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTIQN: SEQ ID NQ: 26:

```
Asn Trp Ser Pro Thr Ala Ala Leu Val Met Ala Gln Leu Leu Arg Ile
1               5                  10                  15

Pro Gln Ala Ile
            20
```

(2) INFORMATIQN FQR SEQ ID NQ: 27:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MQLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTIQN: SEQ ID NQ: 27:

```
Leu Leu Arg Ile Pro Gln Ala Ile Leu Asp Met Ile Ala Gly Ala His
1               5                  10                  15

Trp Gly Val Leu
            20
```

(2) INFQRMATIQN FQR SEQ ID NQ: 28:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TQPQLQGY: linear

(ii) MQLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

```
Ala Gly Ala His Trp Gly Val Leu Ala Gly Leu Ala Tyr Phe Ser Met
1               5                  10                  15

Val Gly Asn Met
            20
```

(2) INFQRMATIQN FOR SEQ ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

```
Val Val Leu Leu Leu Phe Ala Gly Val Asp Ala Glu Thr Ile Val Ser
1               5                  10                  15

Gly Gly Gln Ala
            20
```

(2) INFORMATION FOR SEQ ID NO: 30:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

```
Leu Asn Cys Asn Glu Ser Leu Asn Thr Gly Trp Leu Ala Gly Leu Ile
1               5                  10                  15

Tyr Gln His Lys
            20
```

(2) INFORMATION FOR SEQ ID NO: 31:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

```
Ala Gly Leu Ile Tyr Gln His Lys Phe Asn Ser Ser Gly Cys Pro Glu
1               5                  10                  15

Arg Leu Ala Ser
            20
```

(2) INFORMATION FOR SEQ ID NO: 32:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDMESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEOUENCE DESCRIPTION: SEO ID NO: 32:

```
Gly Cys Pro Glu Arg Leu Ala Ser Cys Arg Pro Leu Thr Asp Phe Asp
1               5                  10                  15

Gln Gly Trp Gly
            20
```

(2) INFORMATION FOR SEO ID NO: 33:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEOUENCE DESCRIPTION: SEQ ID NO: 33:

```
Thr Asp Phe Asp Gln Gly Trp Gly Pro Ile Ser Tyr Ala Asn Gly Ser
1               5                  10                  15

Gly Pro Asp Gln
            20
```

(2) INFORMATION FOR SEO ID NO: 34:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEO ID NO: 34:

```
Ala Asn Gly Ser Gly Pro Asp Gln Arg Pro Tyr Cys Trp His Tyr Pro
1               5                  10                  15

Pro Lys Pro Cys
            20
```

(2) INFORMATION FOR SEQ ID NO: 35:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

```
Trp His Tyr Pro Pro Lys Pro Cys Gly Ile Val Pro Ala Lys Ser Val
1               5                  10                  15

Cya Gly Pro Val
            20
```

(2) INFORMATION FOR SEQ ID NO: 36:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

```
Ala Lys Ser Val Cys Gly Pro Val Tyr Cys Phe Thr Pro Ser Pro Val
1               5                  10                  15

Val Val Gly Thr
            20
```

(2) INFORMATION FOR SEQ ID NO: 37:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

```
Pro Ser Pro Val Val Val Gly Thr Thr Asp Arg Ser Gly Ala Pro Thr
1               5                  10                  15

Tyr Ser Trp Gly
            20
```

(2) INFORMATION FOR SEQ ID NO: 38:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

```
Gln Leu Phe Thr Phe Ser Pro Arg Arg His Trp Thr Thr Gln Gly Cys
1               5                  10                  15

Asn Cys Ser Ile
            20
```

(2) INFORMATION FOR SEQ ID NO: 39:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:

```
Gly Asn Trp Phe Gly Cys Thr Trp Met Asn Ser Thr Gly Phe Thr Lys
1               5                  10                  15

Val Cys Gly Ala
            20
```

(2) INFORMATION FOR SEQ ID NO: 40:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40:

```
Gly Phe Thr Lys Val Cys Gly Ala Pro Pro Cys Val Ile Gly Gly Ala
1               5                  10                  15

Gly Asn Asn Thr
            20
```

(2) INFORMATION FOR SEQ ID NO: 41:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41:

```
Ile Gly Gly Ala Gly Asn Asn Thr Leu His Cys Pro Thr Asp Cys Phe
1               5                  10                  15

Arg Lys His Pro
            20
```

(2) INFORMATION FOR SEQ ID NO: 42:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42:

```
Thr Asp Cys Phe Arg Lys His Pro Asp Ala Thr Tyr Ser Arg Cys Gly
1               5                  10                  15

Ser Gly Pro Trp
            20
```

(2) INFORMATION FOR SEQ ID NO: 43:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43:

```
Ser Arg Cys Gly Ser Gly Pro Trp Ile Thr Pro Arg Cys Leu Val Asp
1               5                  10                  15

Tyr Pro Tyr Arg
            20
```

(2) INFORMATION FOR SEO ID NO: 44:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEOUENCE DESCRIPTION: SEO ID NO: 44:

```
Cys Leu Val Asp Tyr Pro Tyr Arg Leu Trp His Tyr Pro Cys Thr Ile
1               5                  10                  15

Asn Tyr Thr Ile
            20
```

(2) INFORMATION FOR SEO ID NO: 45:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEO ID NO: 45:

```
Pro Cys Thr Ile Asn Tyr Thr Ile Phe Lys Ile Arg Met Tyr Val Gly
1               5                  10                  15

Gly Val Glu His
            20
```

(2) INFORMATION FOR SEQ ID NO: 46:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 46:

```
Ser Gly Leu Val Ser Leu Phe Thr Pro Gly Ala Lye Gln Asn Ile Gln
1               5                  10                  15

Leu Ile Asn Thr
            20
```

(2) INFORMATION FOR SEQ ID NO: 47:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 47:

```
Gln Asn Ile Gln Leu Ile Asn Thr Asn Gly Ser Trp His Ile Asn Ser
1               5                  10                  15

Thr Ala Leu Asn
            20
```

(2) INFORMATION FOR SEQ ID NO: 48:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 68 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 1
(D) OTHER INFORMATION: Xaa is Pro or Gln

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xaa is Asn or Thr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 6
(D) OTHER INFORMATION: Xaa is Arg or His

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 7
(D) OTHER INFORMATION: Xaa is Arg or Lys

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 11
(D) OTHER INFORMATION: Xaa is Leu or Val or Phe

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 13
(D) OTHER INFORMATION: Xaa is Lys or Arg

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 18
(D) OTHER INFORMATION: Xaa is Leu or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 22
(D) OTHER INFORMATION: Xaa is Phe or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 26
(D) OTHER INFORMATION: Xaa is Met or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 27
(D) OTHER INFORMATION: Xaa is Gly or Glu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 31
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 32
(D) OTHER INFORMATION: Xaa is Val or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 34

(D) OTHER INFORMATION: Xaa is Ala or Gly

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 36
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 39
(D) OTHER INFORMATION: Xaa is Ala or Val

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 40
(D) OTHER INFORMATION: Xaa is Ala or Ser

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 41
(D) OTHER INFORMATION: Xaa is Arg or Ala

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 42
(D) OTHER INFORMATION: Xaa is Ala or Thr or Glu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 44
(D) OTHER INFORMATION: Xaa is Ala or Glu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 49
(D) OTHER INFORMATION: Xaa is Val or Ala or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 50
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 51
(D) OTHER INFORMATION: Xaa is Glu or Gly

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 54
(D) OTHER INFORMATION: Xaa is Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 56
(D) OTHER INFORMATION: Xaa is Phe or Tyr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 57
(D) OTHER INFORMATION: Xaa is Ala or Pro

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 61
(D) OTHER INFORMATION: Xaa is Leu or Ile

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 48:

```
Xaa Xaa Asp Pro Arg Xaa Xaa Ser Arg Asn Xaa Gly Xaa Val Ile Asp
1               5                  10                  15

Thr Xaa Thr Cys Gly Xaa Ala Asp Leu Xaa Xaa Tyr Ile Pro Xaa Xaa
            20                  25                  30

Gly Xaa Pro Xaa Gly Gly Xaa Xaa Xaa Xaa Leu Xaa His Gly Val Arg
        35                  40                  45

Xaa Xaa Xaa Asp Gly Xaa Asn Xaa Xaa Thr Gly Asn Xaa Pro Gly Cys
    50                  55                  60

Ser Phe Ser Ile
65
```

(2) INFORMATION FOR SEQ ID NO: 49:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 32 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 1
(D) OTHER INFORMATION: Xaa is Ser or Ala or Gln or Leu or Asn or Tyr or Arg or His

(ix) FEATURE:

(A) NAME/KEY: misc-feature

(B) LOCATION: 2
(D) OTHER INFORMATION: Xaa is Gly or Ser or Thr or Ala or Arg

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Phe or Ile or Leu or Val

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 4
(D) OTHER INFORMATION: Xaa is Val or Ala or Thr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 5
(D) OTHER INFORMATION: Xaa is Ser or Asp or Gly

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 6
(D) OTHER INFORMATION: Xaa is Leu or Ile or Trp or Phe or Met

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 7
(D) OTHER INFORMATION: Xaa is Leu or Ile or Phe

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 8
(D) OTHER INFORMATION: Xaa is Ala or Thr or Asp or Ser

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 9
(D) OTHER INFORMATION: Xaa is Pro or Gln or Ser or Arg or Leu or Ile or Thr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 11
(D) OTHER INFORMATION: Xaa is Ala or Pro or Ser

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 12
(D) OTHER INFORMATION: Xaa is Lys or Ser or Gln or Ala or Arg

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 14
(D) OTHER INFORMATION: Xaa is Asn or Lys or Asp or Arg

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 15
(D) OTHER INFORMATION: Xaa is Val or Ile or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 16
(D) OTHER INFORMATION: Xaa is Gln or Ser or Tyr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 18
(D) OTHER INFORMATION: Xaa is Ile or Val

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 20
(D) OTHER INFORMATION: Xaa is Thr or Ser

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 26
(D) OTHER INFORMATION: Xaa is Leu or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 28
(D) OTHER INFORMATION: Xaa is Ser or Arg

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 49:

```
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Gly Xaa Xaa Gln Xaa Xaa Xaa
1               5                   10                  15

Leu Xaa Asn Xaa Asn Gly Ser Trp His Xaa Asn Xaa Thr Ala Leu Asn
            20                  25                  30
```

(2) INFORMATION FOR SEQ ID NO: 50:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 44 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xaa is Met or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Gly or Glu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 7
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 8
(D) OTHER INFORMATION: Xaa is Val or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 10
(D) OTHER INFORMATION: Xaa is Ala or Gly

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 12
(D) OTHER-INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 15
(D) OTHER INFORMATION: Xaa is Ala or Val

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 16
(D) OTHER INFORMATION: Xaa is Ala or Ser

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 17
(D) OTHER INFORMATION: Xaa Is Arg or Ala

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 18
(D) OTHER INFORMATION: Xaa is Ala or Thr or Glu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 20
(D) OTHER INFORMATION: Xaa is Ala or Glu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 25
(D) OTHER INFORMATION: Xaa is Val or Ala or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 26
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 27
(D) OTHER INFORMATION: Xaa is Glu or Gly

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 30
(D) OTHER INFORMATION: Xaa is Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 32
(D) OTHER INFORMATION: Xaa is Phe or Tyr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 33
(D) OTHER INFORMATION: Xaa is Ala or Pro

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 37
(D) OTHER INFORMATION: Xaa is Leu or Ile

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 50:

```
Leu Xaa Xaa Tyr Ile Pro Xaa Xaa Gly Xaa Pro Xaa Gly Gly Xaa Xaa
1               5                   10                  15

Xaa Xaa Leu Xaa His Gly Val Arg Xaa Xaa Xaa Asp Gly Xaa Asn Xaa
            20                  25                  30

Xaa Thr Gly Asn Xaa Pro Gly Cys Ser Phe Ser Ile
        35                  40
```

(2) INFORMATION FOR SEQ ID NO: 51:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY; misc-feature
(B) LOCATION: 1
(D) OTHER INFORMATION: Xaa is Val or Ala or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xea is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Glu or Gly

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 6
(D) OTHER INFORMATION: Xaa is Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 8
(D) OTHER INFORMATION: Xaa is Phe or Tyr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 9
(D) OTHER INFORMATION: Xaa is Ala or Pro

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 13
(D) OTHER INFORMATION: Xaa is Leu or Ile

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 51:

```
Xaa Xaa Xaa Asp Gly Xaa Asn Xaa Xaa Thr Gly Asn Xaa Pro Gly Cys
1               5                  10                  15

Ser Phe Ser Ile
            20
```

(2) INFORMATION FOR SEQ ID NO: 52:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Ala or Val

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 4
(D) OTHER INFORMATION: Xaa is Ala or Ser

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 5
(D) OTHER INFORMATION: Xaa is Arg or Ala

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 6
(D) OTHER INFORMATION: Xaa is Ala or Thr or Glu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 8
(D) OTHER INFORMATION: Xaa is Ala or Glu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 13

(D) OTHER INFORMATION: Xaa is Val or Ala or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 14
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 15
(D) OTHER INFORMATION: Xaa is Glu or Gly

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 18
(D) OTHER INFORMATION: Xaa is Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 20
(D) OTHER INFORMATION: Xaa is Phe or Tyr

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 52:

```
Xaa Xaa Xaa Asp Gly Xaa Asn Xaa Xaa Thr Gly Asn Xaa Pro Gly Cys
1               5                   10                  15

Ser Phe Ser Ile
            20
```

(2) INFORMATION FOR SEQ ID NO: 53:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xaa is Met or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Gly or Glu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 7
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 8
(D) OTHER INFORMATION: Xaa is Val or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 10
(D) OTHER INFORMATION: Xaa is Ala or Gly

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 12
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 15
(D) OTHER INFORMATION: Xaa is Ala or Val

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 16
(D) OTHER INFORMATION: Xaa is Ala or Ser

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 17
(D) OTHER INFORMATION: Xaa is Arg or Ala

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 18
(D) OTHER INFORMATION: Xaa is Ala or Thr or Glu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 20
(D) OTHER INFORMATION: Xaa is Ala or Glu

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 53:

Leu Xaa Xaa Tyr Ile Pro Xaa Xaa Gly Xaa Pro Xaa Gly Gly Xaa Xaa
1 5 10 15

Xaa Xaa Leu Xaa
20

(2) INFORMATION FOR SEQ ID NO: 54:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 1
(D) OTHER INFORMATION: Xaa is Pro or Gln

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xaa is Asn or Thr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 6
(D) OTHER INFORMATION: Xaa is Arg or His

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 7
(D) OTHER INFORMATION: Xaa is Arg or Lys

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 11
(D) OTHER INFORMATION: Xaa is Leu or Val or Phe

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 13
(D) OTHER INFORMATION: Xaa is Lys or Arg

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 18

(D) OTHER INFORMATION: Xaa is Leu or Ile

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54:

```
Xaa Xaa Asp Pro Arg Xaa Xaa Ser Arg Asn Xaa Gly Xaa Val Ile Asp
1               5                  10                  15

Thr Xaa Thr Cys
            20
```

(2) INFORMATION FOR SEQ ID NO: 55:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 1
(D) OTHER INFORMATION: Xaa is Ser or Ala or Gln or Leu or Asn or Tyr or Arg or His

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xaa is Gly or Ser or Thr or Ala or Arg

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Phe or Ile or Leu or Val

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 4
(D) OTHER INFORMATION: Xaa is Val or Ala or Thr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 5
(D) OTHER INFORMATION: Xaa is Ser or Asp or Gly

(Ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 6
(D) OTHER INFORMATION: Xaa is Leu or Ile or Trp or Phe or Met

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 7
(D) OTHER INFORMATION: Xaa is Leu or Ile or Phe

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: B
(D) OTHER INFORMATION: Xaa is Ala or Thr or Asp or Ser

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 9
(D) OTHER INFORMATION: Xaa is Pro or Gln or Ser or Arg or Leu or Ile or Thr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 11
(D) OTHER INFORMATION: Xaa is Ala or Pro or Ser

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 12
(D) OTHER INFORMATION: Xaa is Lys or Ser or Gln or Ala or Arg

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 14
(D) OTHER INFORMATION: Xaa is Asn or Lys or Asp or Arg

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 15
(D) OTHER INFORMATION: Xaa is Val or Ile or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 16
(D) OTHER INFORMATION: Xaa is Gln or Ser or Tyr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 18
(D) OTHER INFORMATION: Xaa is Ile or Val

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 20

(D) OTHER INFORMATION: Xaa is Thr or Ser

(xi) SEQUENCE OESCRIPTION: SEQ ID NO: 55:

```
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Gly Xaa Xaa Gln Xaa Xaa Xaa
1               5                   10                  15

Leu Xaa Asn Xaa
            20
```

(2) INFORMATION FOR SEQ ID NO: 56:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDBDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY; misc-feature
(B) LOCATION: 2
(O) OTHER INFORMATION: Xaa is Asn or Lys or Asp or Arg

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Val or Ile or Leu

(ix) FEATURE:

(A) NAME/KEY; misc-feature
(B) LOCATION: 4
(D) OTHER INFORMATION: Xaa is Gln or Ser or Tyr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 6
(D) OTHER INFORMATION: Xaa is Ile or Val

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 8
(D) OTHER INFORMATION: Xaa is Thr or Ser

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 14
(O) OTHER INFORMATION: Xaa is Leu or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 16
(D) OTHER INFORMATION: Xaa is Ser or Arg

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 56:

```
Gln Xaa Xaa Xaa Leu Xaa Asn Xaa Asn Gly Ser Trp His Xaa Asn Xaa
1               5                  10                  15

Thr Ale Leu Asn
            20
```

(2) INFORMATION FOR SEQ ID NO: 57:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 278 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 57:

```
Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu Ser Met Glu Thr
1               5                  10                  15

Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser Pro Pro Ala Val
            20                  25                  30

Pro Gln Thr Phe Gln Val Ala His Leu His Ala Pro Thr Gly Ser Gly
        35                  40                  45

Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln Gly Tyr Lys Val
    50                  55                  60

Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr
65                  70                  75                  80

Met Ser Lys Ala His Gly Val Asp Pro Asn Ile Arg Thr Gly Val Arg
                85                  90                  95

Thr Ile Thr Thr Gly Ala Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe
            100                 105                 110

Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys
        115                 120                 125

Asp Glu Cys His Ser Ile Asp Ser Thr Ser Ile Leu Gly Ile Gly Thr
    130                 135                 140

Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala
145                 150                 155                 160

Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His Pro Asn Ile Glu
                165                 170                 175
```

```
Glu Val Ala Leu Ser Ser Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala
            180                 185                 190

Ile Pro Ile Glu Val Ile Lys Gly Gly Arg His Leu Ile Phe Cys His
        195                 200                 205

Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu Ser Gly Phe Gly
    210                 215                 220

Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro
225                 230                 235                 240

Thr Ser Gly Asp Val Val Val Val Ala Thr Asp Ala Leu Met Thr Gly
                245                 250                 255

Phe Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr
            260                 265                 270

Gln Thr Val Asp Phe Ser
        275
```

(2) INFORMATION FOR SEQ ID NO: 58:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 104 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xaa is Arg or Lys

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Ala or Ser or Thr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 5
(D) OTHER INFORMATION: Xaa is Ala or Gly

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 6
(D) OTHER INFORMATION: Xaa Is Gln or Lys or Arg

(ix) FEATURE:

(A) NAME/KEY: misc-feature

(B) LOCATION: 9
(D) OTHER INFORMATION: Xaa is Tyr or His

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 15
(D) OTHER INFORMATION: Xaa is Gly or Ala

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 17
(D) OTHER INFORMATION: Xaa is Glu or Lys

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 19
(D) OTHER INFORMATION: Xaa is Cys or Met or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 21
(D) OTHER INFORMATION: Xaa is Trp or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 34
(D) OTHER INFORMATION: Xaa is Ser or Asn or Thr or Asp or His

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 37
(D) OTHER INFORMATION: Xaa is Pro or Gin

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 38
(D) OTHER INFORMATION: Xaa is Asn or Thr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 42
(D) OTHER INFORMATION: Xaa is Arg or His

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 43
(D) OTHER INFORMATION: Xaa is Arg or Lys

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 47
(D) OTHER INFORMATION: Xaa is Leu or Val or Phe

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 49
(D) OTHER INFORMATION: Xaa is Lys or Arg

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 54
(D) OTHER INFORMATION: Xaa is Leu or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 58
(D) OTHER INFORMATION: Xaa is Phe or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 62
(D) OTHER INFORMATION: Xaa is Met or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 63
(D) OTHER INFORMATION: Xaa is Gly or Glu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 67
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 68
(D) OTHER INFORMATION: Xaa is Val or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 70
(D) OTHER INFORMATION: Xaa is Ala or Gly

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 72
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 75
(D) OTHER INFORMATION: Xaa is Ala or Val

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 76
(D) OTHER INFORMATION: Xaa is Ala or Ser

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 77
(D) OTHER INFORMATION: Xaa is Arg or Ala

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 78
(D) OTHER INFORMATION: Xaa is Ala or Thr or Glu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 80
(D) OTHER INFORMATION: Xaa is Ala or Glu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 85
(D) OTHER INFORMATION: Xaa is Val or Ala or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 86
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 87
(D) OTHER INFORMATION: Xaa is Glu or Gly

(ix) FEATURE:

(A) NAMB/KEY: misc-feature
(B) LOCATION: 90
(D) OTHER INFORMATION: Xaa is Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 92

(D) OTHER INFORMATION: Xaa is Phe or Tyr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 93
(D) OTHER INFORMATION: Xaa is Ala or Pro

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 97
(D) OTHER INFORMATION: Xaa is Leu or Ile

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 58:

```
Gly Xaa Xaa Trp Xaa Xaa Pro Gly Xaa Pro Trp Pro Leu Tyr Xaa Asn
1               5                  10                  15

Xaa Gly Xaa Gly Xaa Ala Gly Trp Leu Leu Ser Pro Arg Gly Ser Arg
            20                  25                  30

Pro Xaa Trp Gly Xaa Xaa Asp Pro Arg Xaa Xaa Ser Arg Asn Xaa Gly
        35                  40                  45

Xaa Val Ile Asp Thr Xaa Thr Cys Gly Xaa Ala Asp Leu Xaa Xaa Tyr
    50                  55                  60

Ile Pro Xaa Xaa Gly Xaa Pro Xaa Gly Gly Xaa Xaa Xaa Xaa Leu Xaa
65                  70                  75                  80

His Gly Val Arg Xaa Xaa Xaa Asp Gly Xaa Asn Xaa Xaa Thr Gly Asn
                85                  90                  95

Xaa Pro Gly Cys Ser Phe Ser Ile
            100
```

(2) INFORMATION FOR SEQ ID NO: 59:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 76 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xaa is Arg or Lys

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Ala or Ser or Thr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 5
(D) OTHER INFORMATION: Xaa is Ale or Gly

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 6
(D) OTHER INFORMATION: Xea is Gln or Lys or Arg

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 9
(D) OTHER INFORMATION: Xea is Tyr or His

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 15
(D) OTHER INFORMATION: Xaa is Gly or Ala

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 17
(D) OTHER INFORMATION: Xaa is Glu or Lys

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 19
(D) OTHER INFORMATION: Xaa is Cys or Met or Leu

(ix) FEATURE:

(A) NAME/KEY; misc-feature
(B) LOCATION: 21
(D) OTHER INFORMATION: Xaa is Trp or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 34
(D) OTHER INFORMATION: Xaa is Ser or Asn or Thr or Asp or His

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 37
(D) OTHER INFORMATION: Xaa is Pro or Gln

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 38
(D) OTHER INFORMATION: Xaa is Asn or Thr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 42
(D) OTHER INFORMATION: Xaa is Arg or His

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 43
(D) OTHER INFORMATION: Xea is Arg or Lys

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 47
(D) OTHER INFORMATION: Xaa is Leu or Val or Phe

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 49
(D) OTHER INFORMATION: Xaa is Lys or Arg

(ix) FEATURE:

(A) NAME/KEY; misc-feature
(B) LOCATION: 54
(D) OTHER INFORMATION: Xaa is Leu or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feeture
(B) LOCATION: 58
(D) OTHER INFORMATION: Xaa is Phe or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 62
(D) OTHER INFORMATION: Xaa is Met or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 63
(D) OTHER INFORMATION: Xaa is Gly or Glu

(ix) FEATURE:

(A) NAME/KEY: misc-feeture
(B) LOCATION: 67
(D) OTHER INFORMATION: Xaa is Leu or Vel or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 68

(D) OTHER INFORMATION; Xaa is Val or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 70
(D) OTHER INFORMATION: Xaa is Ala or Gly

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 72
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 75
(D) OTHER INFORMATION: Xaa is Ala or Val

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 76
(D) OTHER INFORMATION: Xaa is Ala or Ser

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 59:

```
Gly Xaa Xaa Trp Xaa Xaa Pro Gly Xaa Pro Trp Pro Leu Tyr Xaa Asn
1               5                  10                  15

Xaa Gly Xaa Gly Xaa Ala Gly Trp Leu Leu Ser Pro Arg Gly Ser Arg
            20                  25                  30

Pro Xaa Trp Gly Xaa Xaa Asp Pro Arg Xaa Xaa Ser Arg Asn Xaa Gly
        35                  40                  45

Xaa Val Ile Asp Thr Xaa Thr Cys Gly Xaa Ala Asp Leu Xaa Xaa Tyr
    50                  55                  60

Ile Pro Xaa Xaa Gly Xaa Pro Xaa Gly Gly Xaa Xaa
65                  70                  75
```

(2) INFORMATION FOR SEQ ID NO: 60:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 1
(D) OTHER INFORMATION: Xaa is Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Phe or Tyr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 4
(D) OTHER INFORMATION: Xaa is Ala or Pro

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 8
(D) OTHER INFORMATION: Xaa is Leu or Ile

(xi) SEOUENCE DESCRIPTION: SEO ID NO: 60:

```
Xaa Asn Xaa Xaa Thr Gly Asn Xaa Pro Gly Cys Ser Phe Ser Ile
1               5                  10                  15
```

(2) INFORMATION FOR SEO ID NO: 61:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xaa is Phe or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 6
(D) OTHER INFORMATION: Xaa is Met or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 7
(D) OTHER INFORMATION: Xaa is Gly or Glu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 11

(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 12
(D) OTHER INFORMATION: Xaa is Val or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 14
(D) OTHER INFORMATION: Xaa is Ala or Gly

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 16
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 61:

```
Gly Xaa Ala Asp Leu Xaa Xaa Tyr Ile Pro Xaa Xaa Gly Xaa Pro Xaa
1               5                  10                  15
```

(2) INFORMATION FOR SEQ ID NO: 62:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16 amino acids
(B) TYPE: amino acid
(C) STRAHDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xaa is Met or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Gly or Glu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 7
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 8
(D) OTHER INFORMATION: Xaa is Val or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 10
(D) OTHER INFORMATION: Xaa is Ala or Gly

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 12
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 15
(D) OTHER INFORMATION: Xaa is Ala or Val

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 62:

```
Gly Xaa Ala Asp Leu Xaa Xaa Tyr Ile Pro Xaa Xaa Gly Xaa Pro Xaa
1               5                  10                  15
```

(2) INFORMATION FOR SEQ ID NO: 63:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 1
(D) OTHER INFORMATION: Xaa is Met or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xaa is Gly or Glu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 6
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 7
(D) OTHER INFORMATION: Xaa is Val or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 9
(D) OTHER INFORMATION: Xaa is Ala or Gly

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 11
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 14
(D) OTHER INFORMATION: Xaa is Ala or Val

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 63:

```
Xaa Xaa Tyr Ile Pro Xaa Xaa Gly Xaa Pro Xaa Gly Gly Xaa
1               5                   10
```

(2) INFORMATION FOR SEQ ID NO: 64:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 4
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 5
(D) OTHER INFORMATION: Xaa is Val or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 7
(D) OTHER INFORMATION: Xaa is Ala or Gly

(ix) FEATURE:

(A) NAMB/KEY: misc-feature
(B) LOCATION: 9
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(xi) SEQUENCE DESCRIPTION: SEO ID NO: 64:

```
Tyr Ile Pro Xaa Xaa Gly Xaa Pro Xaa
1               5
```

(2) INFORMATION FOR SEQ ID NO: 65:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 4
(D) OTHER INFORMATION: Xaa is Val or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 6
(D) OTHER INFORMATION: Xaa is Ala or Gly

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: B
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(xi) SEQUENCE DESCRIPTION: SEO ID NO: 65:

```
Ile Pro Xaa Xaa Gly Xaa Pro Xaa
1               5
```

(2) INFORMATION FOR SEO ID NO: 66:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 1
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xae is Val or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 4
(D) OTHER INFORMATION: Xae is Ala or Gly

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 6
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 9
(D) OTHER INFORMATION: Xaa is Ala or Val

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 66:

```
Xaa Xaa Gly Xaa Pro Xaa Gly Gly Xaa
1               5
```

(2) INFORMATION FOR SEQ ID NO: 67:

(i) SEQUENCE CHARACTERISTICS;

(A) LENGTH: 44 amino acids
(B) TYPE: amino ecid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 67:

```
Leu Met Gly Tyr Ile Pro Leu Val Gly Ala Pro Leu Gly Gly Ala Ala
1               5                   10                  15
```

```
Arg Ala Leu Ala His Gly Val Arg Val Leu Glu Asp Gly Val Asn Tyr
                20                  25                  30

Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe Ser Ile
        35                  40
```

(2) INFORMATION FOR SEO ID NO: 68:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 1
(D) OTHER INFORMATION: Xaa is Val or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Ala or Gly

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 5
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 8
(D) OTHER INFORMATION: Xaa is Ala or Val

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 68:

```
Xaa Gly Xaa Pro Xaa Gly Gly Xaa
1               5
```

(2) INFORMATION FOR SEO ID NO: 69:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 69:

```
Leu Met Gly Tyr Ile Pro Leu Val
1               5
```

(2) INFORMATION FOR SEQ ID NO: 70:

(i) SEQUENCE CHARACTERISTICS;

(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDMESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 70:

```
Met Gly Tyr Ile Pro Leu Val
1               5
```

(2) INFORMATION FOR SEQ ID NO: 71:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 71:

```
Tyr Ile Pro Leu Val Gly Ala Pro Leu
1               5
```

(2) INFORMATION FOR SEQ ID NO: 72:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 72:

```
Ile Pro Leu Val Gly Ala Pro Leu
1               5
```

(2) INFORMATION FOR SEQ ID NO: 73:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 73:

```
Val Leu Glu Asp Ile Val Asn Tyr Ala Thr Gly Asn Leu Pro Gly Cys
1               5                  10                  15

Ser Phe Ser Ile
            20
```

(2) INFORMATION FOR SEQ ID NO: 74:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xaa is Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 4
(D) OTHER INFORMATION: Xaa is Phe or Tyr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 5
(D) OTHER INFORMATION: Xaa is Ala or Pro

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 9
(D) OTHER INFORMATION: Xaa is Leu or Ila

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 74:

```
Gly Xaa Asn Xaa Xaa Thr Gly Asn Xaa
1               5
```

(2) INFORMATION FOR SEQ ID NO: 75:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDMESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 1
(D) OTHER INFORMATION: Xaa is Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Phe or Tyr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 4
(D) OTHER INFORMATION: Xaa is Ala or Pro

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 8
(D) OTHER INFORMATION: Xaa is Leu or Ile

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 75:

```
Xaa Asn Xaa Xaa Thr Gly Asn Xaa
1               5
```

(2) INFORMATION FOR SEQ ID NO: 76:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xaa is Leu or Ile

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76:

Asn Xaa Pro Gly Cys Ser Phe Ser Ile
1 5

(2) INFORMATION FOR SEQ ID NO: 77:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 1
(O) OTHER INFORMATION: Xaa is Leu or Ile

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 77:

Xaa Pro Gly Cys Ser Phe Ser Ile
1 5

(2) INFORMATION FOR SEQ ID NO: 78:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 78:

Gly Val Asn Tyr Ala Thr Gly Asn Leu
1 5

(2) INFORMATION FOR SEQ ID NO: 79:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 79:

Gly Val Asn Tyr Ala Thr Gly Asn Leu
1 5

(2) INFORMATION FOR SEO ID NO: 80:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEOUENCE DESCRIPTION: SEQ ID NO: 80:

Asn Leu Pro Gly Cys Ser Phe Ser Ile
1 5

(2) INFORMATION FOR SEO ID NO: 81:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEOUENCE DESCRIPTION: SEO ID NO: 81:

Leu Pro Gly Cys Ser Phe Ser Ile
1 5

(2) INFORMATION FOR SEO ID NO: 82:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 1
(D) OTHER INFORMATION: Xaa is Ala or Thr or Glu

(ix) FEATURE:

(A) NAME/KEY: misc-feature

(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Ala or Glu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 8
(D) OTHER INFORMATION: Xea is Vel or Ala or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 9
(D) OTHER INFORMATION: Xaa Is Leu or Val or Ile

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 82:

```
Xaa Leu Xaa His Gly Val Arg Xaa Xaa
1               5
```

(2) INFORMATION FOR SEQ ID NO: 83:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xaa is Ala or Glu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 7
(D) OTHER INFORMATION: Xaa is Val or Ala or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 8
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 83:

```
Leu Xaa Hie Gly Val Arg Xaa Xaa
1               5
```

(2) INFORMATION FOR SEQ ID NO: 84:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 4
(D) OTHER INFORMATION: Xaa is Val or Ala or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 5
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 6
(D) OTHER INFORMATION: Xaa is Glu or Gly

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 9
(D) OTHER INFORMATION: Xaa is Val or Ile

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 84:

```
Gly Val Arg Xaa Xaa Xaa Asp Gly Xaa
1               5
```

(2) INFORMATION FOR SEQ ID NO: 85:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Val or Ala or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 4
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 5
(D) OTHER INFORMATION: Xaa is Glu or Gly

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 8
(D) OTHER INFORMATION: Xaa is Val or Ile

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 85:

```
Val Arg Xaa Xaa Xaa Asp Gly Xaa
1               5
```

(2) INFORMATION FOR SEQ ID NO: 86:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xaa is Val or Ala or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 4
(D) OTHER INFORMATION: Xaa is Glu or Gly

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 7
(D) OTHER INFORMATION: Xaa is Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 9
(D) OTHER INFORMATION: Xaa is Phe or Tyr

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 86:

```
Arg Xaa Xaa Xaa Asp Gly Xaa Asn Xaa
1               5
```

(2) INFORMATION FOR SEQ ID NO: 87:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: lineer

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY; misc-feature
(B) LOCATION: 1
(D) OTHER INFORMATION: Xaa is Val or Ala or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xaa is Leu or Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Glu or Gly

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 6
(D) OTHER INFORMATION: Xaa is Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 8
(D) OTHER INFORMATION: Xea is Phe or Tyr

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 87:

```
Xaa Xaa Xaa Asp Gly Xaa Asn Xaa
1               5
```

(2) INFORMATION FOR SEQ ID NO: 88:

(i) SEQUENCE CHARACTERISTICS;

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TQPQLQGY: linear

(ii) MQLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTIQN: SEQ ID NQ: 88:

```
Ala Leu Ala His Gly Val Arg Val Leu
1               5
```

(2) INFQRMATIQN FQR SEQ ID NQ: 89:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MQLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 89:

```
Leu Ala His Gly Val Arg Val Leu
1               5
```

(2) INFORMATION FOR SEQ ID NO: 90:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TQPQLQGY: linear

(ii) MQLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTIQN: SEQ ID NQ: 90:

```
Val Arg Val Leu Glu Asp Gly Val
1               5
```

(2) INFQRMATIQN FQR SEQ ID NQ: 91:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TQPQLQGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 91:

Arg Val Leu Glu Asp Gly Val
1 5

(2) INFORMATION FOR SEQ ID NO: 92:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 92:

Val Leu Glu Asp Gly Val Asn Tyr
1 5

(2) INFORMATION FOR SEQ ID NO: 93:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 93:

Leu Glu Asp Gly Val Asn Tyr
1 5

(2) INFORMATION FOR SEQ ID NO: 94:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 emino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 94:

Leu Val Gly Ala Pro Leu Gly Gly Ala
1 5

(2) INFORMATION FOR SEQ ID NO: 95:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: B amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TQPQLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 95:

```
Val Gly Ala Pro Leu Gly Gly Ala
1               5
```

(2) INFORMATION FOR SEQ ID NO: 96:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xaa is Leu or Val or Phe

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 4
(D) OTHER INFORMATION: Xaa is Lys or Arg

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 9
(D) OTHER INFORMATION: Xaa is Leu or Ile

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 96:

```
Asn Xaa Gly Xaa Val Ile Asp Thr Xaa
1               5
```

(2) INFORMATION FOR SEQ ID NO: 97:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 1
(D) OTHER INFORMATION: Xaa is Leu or Val or Phe

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Lys or Arg

(lx) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 8
(D) OTHER INFORMATION: Xea is Leu or Ile

(xi) SEOUENCE DESCRIPTION: SEO ID NO: 97:

```
Xaa Gly Xaa Val Ile Asp Thr Xaa
1               5
```

(2) INFORMATION FOR SEO ID NO: 98:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEOUENCE DESCRIPTION: SEO ID NO: 98:

```
Asn Leu Gly Lys Val Ile Asp Thr Leu
1               5
```

(2) INFORMATION FOR SEO ID NO: 99:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: emino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xaa is Arg or Lys

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Ala or Ser or Thr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 5
(D) OTHER INFORMATION: Xaa is Ala or Gly

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 6
(D) OTHER INFORMATION: Xaa is Gin or Lys or Arg

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 9
(D) OTHER INFORMATION: Xaa is Tyr or His

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 15
(D) OTHER INFORMATION: Xaa is Gly or Ala

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 17
(D) OTHER INFORMATION: Xaa is Glu or Lys

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 19
(D) OTHER INFORMATION: Xaa is Cys or Met or Leu

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 99:

```
Gly Xaa Xaa Trp Xaa Xaa Pro Gly Xaa Pro Trp Pro Leu Tyr Xaa Asn
1               5                   10                  15

Xaa Gly Xaa Gly
            20
```

(2) INFORMATION FOR SEQ ID NO: 100:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDBDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 1
(D) OTHER INFORMATION: Xaa is Ala or Ser or Thr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Ala or Gly

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 4
(D) OTHER INFORMATION: Xaa is Gln or Lys or Arg

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 7
(D) OTHER INFORMATION: Xaa is Tyr or His

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 100:

```
Xaa Trp Xaa Xaa Pro Gly Xaa Pro Trp
1               5
```

(2) INFORMATION FOR SEO ID NO: 101:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(O) OTHER INFORMATION: Xaa is Ala or Gly

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3

(D) OTHER INFORMATION: Xaa is Gln or Lys or Arg

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 6
(D) OTHER INFORMATION: Xaa is Tyr or His

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 101:

```
Trp Xaa Xaa Pro Gly Xaa Pro Trp
1               5
```

(2) INFORMATION FOR SEQ ID NO: 102:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 102:

```
Thr Trp Ala Gln Pro Gly Tyr Pro Trp
1               5
```

(2) INFORMATION FOR SEQ ID NO: 103:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRAMDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 103:

```
Trp Ala Gln Pro Gly Tyr Pro Trp
1               5
```

(2) INFORMATION FOR SEQ ID NO: 104:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 147 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 104:

```
Thr Pro Thr Val Ala Thr Thr Arg Asp Gly Lys Leu Pro Ala Thr Gln
1               5                  10                  15

Leu Arg Arg His Ile Asp Leu Leu Val Gly Ser Ala Thr Leu Cys Ser
            20                  25                  30

Ala Leu Tyr Val Gly Asp Leu Cys Gly Ser Val Gln Leu Phe Thr Phe
        35                  40                  45

Ser Pro Arg Arg His Trp Thr Thr Gln Gly Cys Asn Cys Ser Ile Tyr
    50                  55                  60

Pro Gly His Ile Thr Gly His Arg Met Ala Trp Asp Met Met Met Asn
65                  70                  75                  80

Trp Ser Pro Thr Ala Ala Leu Val Met Ala Gln Leu Leu Arg Ile Pro
                85                  90                  95

Gln Ala Ile Leu Asp Met Ile Ala Gly Ala His Trp Gly Val Leu Ala
            100                 105                 110

Gly Ile Ala Tyr Phe Ser Met Val Gly Asn Met Ala Lys Val Leu Val
        115                 120                 125

Val Leu Leu Leu Phe Ala Gly Val Asp Ala Glu Thr Ile Val Ser Gly
    130                 135                 140

Gly Gln Ala
145
```

(2) INFORMATION FOR SEQ ID NO: 105:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 105:

```
Thr Pro Thr Val Ala Thr Thr Arg Asp Gly Lys Leu Pro Ala Thr Gln
1               5                  10                  15

Leu Arg
```

(2) INFORMATION FOR SEQ ID NO: 106:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 76 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 106:

```
Leu Pro Ala Thr Gln Leu Arg Arg His Ile Asp Leu Leu Val Gly Ser
1               5                   10                  15

Ala Thr Leu Cye Ser Ale Leu Tyr Val Gly Asp Leu Cys Gly Ser Val
            20                  25                  30

Gln Leu Phe Thr Phe Ser Pro Arg Arg His Trp Thr Thr Gln Gly Cys
        35                  40                  45

Asn Cys Ser Ile Tyr Pro Gly His Ile Thr Gly Hie Arg Met Ala Trp
    50                  55                  60

Asp Met Met Met Asn Trp Ser Pro Thr Ale Ale Leu
65                  70                  75
```

(2) INFORMATION FOR SEO ID NO: 107:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 69 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEOUENCE DESCRIPTION: SEO ID NO: 107:

```
Met Asn Trp Ser Pro Thr Ala Ala Leu Val Met Ala Gln Leu Leu Arg
1               5                   10                  15

Ile Pro Gln Ala Ile Leu Asp Met Ile Ala Gly Ala Hie Trp Gly Val
            20                  25                  30

Leu Ala Gly Ile Ala Tyr Phe Ser Met Vel Gly Asn Met Ala Lys Val
        35                  40                  45

Leu Val Vel Leu Leu Leu Phe Ale Gly Vel Asp Ala Glu Thr Ile Vel
    50                  55                  60

Ser Gly Gly Gln Ala
65
```

(2) INFORMATION FOR SEO ID NO: 108:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 70 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature

(B) LOCATION: 2
(D) OTHER INFORMATION: Xaa is Gly or Arg

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Gly or Ala or Lys

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 4
(D) OTHER INFORMATION: Xaa is Ala or Val or Gly or Ser or Asp

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 5
(D) OTHER INFORMATION: Xaa is Gly or Phe or Tyr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 7
(D) OTHER INFORMATION: Xaa is Asn or His or Arg or Leu or Ala or Ser

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 8
(D) OTHER INFORMATION: Xaa is Thr or Ser

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 9
(D) OTHER INFORMATION: Xaa is Met or Ile

(ix) FEATURE:

(A) NAME/KEY; misc-feature
(B) LOCATION: 10
(D) OTHER INFORMATION: Xaa is Asp

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 12
(D) OTHER INFORMATION: Xaa is His or Leu or Val or Thr or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 21
(D) OTHER INFORMATION: Xaa is His or Tyr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 23
(D) OTHER INFORMATION: Xaa is Asp or Glu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 24
(D) OTHER INFORMATION: Xaa is Ala or Thr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 27
(D) OTHER INFORMATION: Xaa is Ser or Thr or Ile or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 28
(D) OTHER INFORMATION: Xaa is Arg or Lys

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 31
(D) OTHER INFORMATION: Xaa is Ser or Ala

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 34
(D) OTHER INFORMATION: Xaa is Trp or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 35
(D) OTHER INFORMATION: Xaa is Ile or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 40
(D) OTHER INFORMATION: Xaa is Leu or Met or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 41
(D) OTHER INFORMATION: Xaa is Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 54
(D) OTHER INFORMATION: Xaa is Ile or Val or Phe or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 56
(D) OTHER INFORMATION: Xaa is Tyr or Phe

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 57
(D) OTHER INFORMATION: Xaa is Thr or Ser or Ala

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 58
(D) OTHER INFORMATION: Xaa is Ile or Val

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 61
(D) OTHER INFORMATION: Xaa is Ile or Val or Ala

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 64
(D) OTHER INFORMATION: Xaa is Tyr or Phe

(xi) SEOUENCE DESCRIPTION: SEQ ID NO: 108:

```
Ile Xaa Xaa Xaa Xaa Asn Xaa Xaa Glx Glx Leu Xaa Cys Pro Thr Asp
1               5                   10                  15

Cya Phe Arg Lys Xaa Pro Xaa Xaa Thr Tyr Xaa Xaa Cys Gly Xaa Gly
            20                  25                  30

Pro Xaa Xaa Thr Pro Arg Cys Xaa Xaa Asp Tyr Pro Tyr Arg Leu Trp
        35                  40                  45

His Tyr Pro Cys Thr Xaa Asn Xaa Xaa Xaa Phe Lys Xaa Arg Met Xaa
    50                  55                  60

Val Gly Gly Val Glu His
65                  70
```

(2) INFORMATION FOR SEQ ID NO: 109:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 1
(D) OTHER INFORMATION: Xaa is Gln or Ser or Tyr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is lie or Val

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 5
(D) OTHER INFORMATION: Xaa is Thr or Ser

(xi) SEOUENCE DESCRIPTION: SEO ID NO: 109:

```
Xaa Leu Xaa Asn Xaa Asn Gly Ser Trp
1               5
```

(2) INFORMATION FOR SEO ID NO: 110:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xaa is Ile or Val

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 4
(D) OTHER INFORMATION: Xaa is Thr or Ser

(xi) SEOUENCE DESCRIPTION: SEO ID NO: 110:

```
Leu Xaa Asn Xaa Asn Gly Ser Trp
1               5
```

(2) INFORMATION FOR SEO ID NO: 111:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 4
(D) OTHER INFORMATION: Xaa is Leu or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 6
(D) OTHER INFORMATION: Xaa is Ser or Arg

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 111:

Ser Trp His Xaa Asn Xaa Thr Ala Leu
1 5

(2) INFORMATION FOR SEQ ID NO: 112:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 4
(D) OTHER INFORMATION: Xaa is Leu or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 6
(D) OTHER INFORMATION: Xaa is Ser or Arg

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 112:

Ser Trp His Xaa Asn Xaa Thr Ala Leu
1 5

(2) INFORMATION FOR SEQ ID NO: 113:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MQLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 113:

Gln Leu Ile Asn Thr Asn Gly Ser Trp
1 5

(2) INFORMATION FOR SEO ID NO: 114:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEO ID NO: 114:

Leu Ile Asn Thr Asn Gly Ser Trp
1 5

(2) INFORMATION FOR SEO ID NO: 115:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 115:

Ser Trp His Ile Asn Ser Thr Ala Leu
1 5

(2) INFORMATION FOR SEO ID NO: 116:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 116:

```
Trp His Ile Asn Ser Thr Ala Leu
1               5
```

(2) INFORMATION FOR SEQ ID NO: 117:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 117:

```
Trp His Ile Asn Ser Thr Ala Leu
1               5
```

(2) INFORMATION FOR SEQ ID NO: 118:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 118:

```
Gly Gly Val Ala Ala Arg Ala Leu Ala His Gly Val Arg Val Leu Glu
1               5                   10                  15

Asp Gly Val Asn Tyr
            20
```

(2) INFORMATION FOR SEQ ID NO: 119:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 1
(D) OTHER INFORMATION: Xaa is Thr or Ser

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xaa is Met or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Asp

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 5
(D) OTHER INFORMATION: Xaa is His or Leu or Val or Thr or Ile

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 119:

```
Xaa Glx Glx Leu Xaa Cys Pro Thr Asp Cys Phe
1               5                  10
```

(2) INFORMATION FOR SEQ ID NO: 120:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 4
(D) OTHER INFORMATION: Xaa is His or Tyr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 6
(D) OTHER INFORMATION: Xaa is Asp or Glu

(ix) FEATURE:

(A) NAME/KEY: mist-feature
(B) LOCATION: 7
(D) OTHER INFORMATION: Xaa is Ala or Thr

(xl) SEQUENCE DESCRIPTION: SEQ ID NO: 120:

```
Phe Arg Lys Xaa Pro Xaa Xaa Thr Tyr
1               5
```

(2) INFORMATION FOR SEQ ID NO: 121:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 1
(D) OTHER INFORMATION: Xaa is Trp or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xaa is Ile or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 7
(D) OTHER INFORMATION: Xaa is Leu or Met or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 8
(D) OTHER INFORMATION: Xaa is Val or Ile

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 121:

```
Xaa Xaa Thr Pro Arg Cys Xaa Xaa
1               5
```

(2) INFORMATION FOR SEQ ID NO: 122:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 1
(D) OTHER INFORMATION: Xaa is Leu or Met or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xaa is Val or Ile

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 122:

```
Xaa Xaa Asp Tyr Pro Tyr Arg Leu
1               5
```

(2) INFORMATION FOR SEQ ID NO: 123:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 1
(D) OTHER INFORMATION: Xaa is Val or Ile

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 123:

```
Xaa Asp Tyr Pro Tyr Arg Leu Trp
1               5
```

(2) INFORMATION FOR SEQ ID NO: 124:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 124:

```
Tyr Pro Tyr Arg Leu Trp His Tyr
1               5
```

(2) INFORMATION FOR SEQ ID NO: 125:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feeture
(B) LOCATION: 8
(D) OTHER INFORMATION: Xaa is Ile or Val or Phe or Leu

(xi) SEOUENCE DESCRIPTION: SEO ID NO: 125:

```
Leu Trp His Tyr Pro Cys Thr Xaa
1               5
```

(2) INFORMATION FOR SEO ID NO: 126:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 1
(D) OTHER INFORMATION: Xea is Ile or Val or Phe or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Tyr or Phe

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 4
(D) OTHER INFORMATION: Xaa is Thr or Ser or Ala

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 5
(D) OTHER INFORMATION: Xaa is Ile or Val

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 8
(D) OTHER INFORMATION: Xaa is Ile or Val or Ala

(xi) SEOUENCE DESCRIPTION: SEO ID NO: 126:

Xaa Asn Xaa Xaa Xaa Phe Lys Xaa
1 5

(2) INFORMATION FOR SEQ ID NO: 127:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 1
(D) OTHER INFORMATION: Xaa is Tyr or Phe

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xaa is Thr or Ser or Ala

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Ile or Val

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 6
(D) OTHER INFORMATION: Xaa is Ile or Val or Ala

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 127:

Xaa Xaa Xaa Phe Lys Xaa Arg Met
1 5

(2) INFORMATION FOR SEQ ID NO: 128:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids.
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 1
(D) OTHER INFORMATION: Xaa is Ile or Val

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 4
(D) OTHER INFORMATION: Xaa is Ile or Val or Ala

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 7
(D) OTHER INFORMATION: Xaa is Tyr or Phe

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 128:

```
Xaa Phe Lys Xaa Arg Met Xaa Val
1               5
```

(2) INFORMATION FOR SEQ ID NO: 129:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRAMDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 1
(D) OTHER INFORMATION: Xaa is Ile or Val or Ala

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 4
(D) OTHER INFORMATION: Xaa is Tyr or Phe

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 129:

```
Xaa Arg Met Xaa Val Gly Gly Val
1               5
```

(2) INFORMATION FOR SEQ ID NO: 130:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xaa is Gly or Arg

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Gly or Ala or Lys

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 4
(D) OTHER INFORMATION: Xaa is Ala or Val or Gly or Ser or Asp

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 5
(D) OTHER INFORMATION: Xaa is Gly or Phe or Tyr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 7
(D) OTHER INFORMATION: Xaa is Asn or His or Arg or Leu or Ala or Ser

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 8
(D) OTHER INFORMATION: Xaa is Thr or Ser

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 9
(D) OTHER INFORMATION: Xaa is Met or Ile

(ix) FEATURE:

(A) MAME/KEY: misc-feature
(B) LOCATION: 10
(D) OTHER INFORMATION: Xaa is Asp

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 12
(D) OTHER INFORMATION: Xaa is His or Leu or Val or Thr or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 21
(D) OTHER INFORMATION: Xaa is His or Tyr

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 130:

```
Ile Xaa Xaa Xaa Xaa Asn Xaa Xaa Glx Glx Leu Xaa Cys Pro Thr Asp
1               5                   10                  15

Cys Phe Arg Lys Xaa Pro
            20
```

(2) INFORMATION FOR SEQ ID NO: 131:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 7
(D) OTHER INFORMATION: Xaa is His or Tyr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 9
(D) OTHER INFORMATION: Xaa is Asp or Glu

(ix) FEATURE:

(A) NAME/KEY: tnisc-feature
(B) LOCATION: 10
(D) OTHER INFORMATION: Xaa is Ala or Thr

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 13
(D) OTHER INFORMATION: Xaa is Ser or Thr or Ile or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 14
(D) OTHER INFORMATION: Xaa is Arg or Lys

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 17
(D) OTHER INFORMATION: Xaa is Ser or Ala

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 20
(D) OTHER INFORMATION: Xaa is Trp or Leu

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 131:

```
Thr Asp Cys Phe Arg Lys Xaa Pro Xaa Xaa Thr Tyr Xaa Xaa Cys Gly
1               5                  10                  15

Xaa Gly Pro Xaa
            20
```

(2) INFORMATION FOR SEQ ID NO: 132:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 1
(D) OTHER INFORMATION: Xea is Ser or Thr or Ile or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xaa is Arg or Lys

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 5
(O) OTHER INFORMATION: Xaa is Ser or Ala

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: B
(D) OTHER INFORMATION: Xaa is Trp or Leu

(lx) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 9

(O) OTHER INFORMATION: Xaa is Ile or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 14
(D) OTHER INFORMATION: Xaa is Leu or Met or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 15
(D) OTHER INFORMATION: Xaa is Val or Ile

(xi) SEQUENCE DESCRIPTION: SEO ID NO: 132:

```
Xaa Xaa Cys Gly Xaa Gly Pro Xaa Xaa Thr Pro Arg Cys Xaa Xaa Asp
1               5                  10                  15

Tyr Pro Tyr Arg
            20
```

(2) INFORMATION FOR SEQ ID NO: 133:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY; misc-feature
(B) LOCATION: 2
(D) OTHER INFORMATION: Xea is Leu or Met or Ile

(ix) FEATURE:

(A) NAME/KEY; misc-feature
(B) LOCATION: 3
(D) OTHER INFORMATION: Xaa is Val or Ile

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION; 16
(D) OTHER INFORMATION: Xaa is Ile or Val or Phe or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 18
(D) OTHER INFORMATION: Xaa is Tyr or Phe

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 19
(D) OTHER INFORMATION: Xaa is Thr or Ser or Ala

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 20
(D) OTHER INFORMATION: Xaa is Ile or Val

(xi) SEOUENCE DESCRIPTION: SEQ ID NO: 133:

```
Cys Xaa Xaa Asp Tyr Pro Tyr Arg Leu Trp His Tyr Pro Cys Thr Xaa
1               5                  10                  15

Asn Xaa Xaa Xaa
            20
```

(2) INFORMATION FOR SEO ID NO: 134:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 20 amino acids
(B) TYPE: amino acid
(C) STRANDEONESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 4
(D) OTHER INFORMATION: Xaa is Ile or Val or Phe or Leu

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 6
(D) OTHER INFORMATION: Xaa is Tyr or Phe

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 7
(D) OTHER INFORMATION: Xaa is Thr or Ser or Ala

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 8
(D) OTHER INFORMATION: Xaa is Ile or Val

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 11
(D) OTHER INFORMATION: Xaa is Ile or Val or Ala

(ix) FEATURE:

(A) NAME/KEY: misc-feature
(B) LOCATION: 14
(D) OTHER INFORMATION: Xaa is Tyr or Phe

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 134:

```
Pro Cys Thr Xaa Asn Xaa Xaa Xaa Phe Lya Xaa Arg Met Xaa Val Gly
1               5                   10                  15

Gly Val Glu His
            20
```

(2) INFORMATION FOR SEQ ID NO: 135:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 135:

```
Val Ala Lys Ala Val Asp Phe Val
1               5
```

(2) INFORMATION FOR SEQ ID NO: 136:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEOUENCE DESCRIPTION: SEQ ID NO: 136:

```
Val Ala Lys Ala Val Asp Phe Ile
1               5
```

(2) INFORMATION FOR SEQ ID NO: 137:

(I) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids

(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 137:

```
Val Glu Ser Met Glu Thr Thr Met
1               5
```

(2) INFORMATION FOR SEQ ID NO: 138:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 138:

```
Ala Val Pro Gln Thr Phe Gln Val
1               5
```

(2) INFORMATION FOR SEQ ID NO: 139:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 139:

```
Tyr Ala Ala Gln Gly Tyr Lys Val
1               5
```

(2) INFORMATION FOR SEQ ID NO: 140:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 140:

Val Leu Val Leu Asn Pro Ser Val Ala
1 5

(2) INFORMATION FQR SEQ ID NQ: 141:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLQGY: linear

(ii) MQLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTIQN: SEQ ID NQ: 141:

Tyr Met Ser Lys Ala His Gly Val
1 5

(2) INFORMATION FOR SEQ ID NO: 142:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TQPQLQGY: linear

(ii) MQLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 142:

Ile Arg Thr Gly Val Arg Thr Ile
1 5

(2) INFORMATION FOR SEQ ID NO: 143:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TQPQLQGY: linear

(ii) MQLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTIQN: SEQ ID NQ: 143:

Tyr Ser Thr Tyr Gly Lys Phe Leu
1 5

(2) INFORMATIQN FQR SEQ ID NO: 144:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 144:

```
Ile Leu Gly Ile Gly Thr Val Leu
1               5
```

(2) INFORMATION FOR SEQ ID NO: 145:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(Xi) SEQUENCE DESCRIPTION: SEQ ID NO: 145:

```
Val Thr Val Pro His Pro Asn Ile
1               5
```

(2) INFORMATION FOR SEQ ID NO: 146:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 146:

```
Ile Pro Phe Tyr Gly Lys Ala Ile
1               5
```

(2) INFORMATION FOR SEQ ID NO: 147:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEOUENCE DESCRIPTION: SEO ID NO: 147:

Phe Tyr Gly Lys Ala Ile Pro Ile
1 5

(2) INFORMATION FOR SEO ID NO: 148:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEOUENCE DESCRIPTION: SEO ID NO: 148:

Val Ile Lys Gly Gly Arg His Leu
1 5

(2) INFORMATION FOR SEO ID NO: 149:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDBDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 149:

Ile Lys Gly Gly Arg His Leu Ile
1 5

(2) INFORMATION FOR SEO ID NO: 150:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEOUENCE DESCRIPTION: SEQ ID NO: 150:

Phe Cys His Ser Lys Lys Lys Cys
1 5

(2) INFORMATION FOR SEQ ID NO: 151:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 151:

```
Cys Asp Glu Leu Ala Ala Lys Leu
1               5
```

(2) INFORMATION FOR SEQ ID NO: 152:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 152:

```
Leu Ala Ala Lys Leu Ser Gly Phe Gly
1               5
```

(2) INFORMATION FOR SEQ ID NO: 153:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 153:

```
Ser Gly Phe Gly Ile Asn Ala Val
1               5
```

(2) INFORMATION FOR SEQ ID NO: 154:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 154:

Phe Gly Ile Asn Ala Val Ala Tyr
1 5

(2) INFORMATION FOR SEQ ID NO: 155:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 155:

Tyr Arg Gly Leu Asp Val Ser Val
1 5

(2) INFORMATION FOR SEQ ID NO: 156:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 156:

Val Ile Pro Thr Ser Gly Asp Val
1 5

(2) INFORMATION FOR SEQ ID NO: 157:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 157:

Ile Pro Thr Ser Gly Asp Val Val
1 5

(2) INFORMATION FOR SEQ ID NO: 158:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEO ID ND: 158:

Val Val Val Ala Thr Asp Ala Leu
1 5

(2) INFORMATION FDR SEO ID-NO: 159:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MDLECULE TYPE: peptide

(xi) SEOUENCE DESCRIPTION: SEO ID NO: 159:

Val Val Ala Thr Asp Ala Leu Met
1 5

(2) INFORMATION FOR SEO ID NO: 160:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEOUENCE DESCRIPTIDN: SEQ ID NO: 160:

Met Thr Gly Phe Thr Gly Asp Phe
1 5

(2) INFORMATION FOR SEO ID NO: 161:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEO ID NO: 161:

Phe Thr Gly Asp Phe Asp Ser Val
1 5

(2) INFORMATION FOR SEO ID NO: 162:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEOUENCE DESCRIPTION: SEO ID NO: 162:

Val Ile Asp Cys Asn Thr Cys Val
1 5

(2) INFORMATION FOR SEO ID NO: 163:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEOUENCE DESCRIPTION: SEO ID NO: 163:

Ala Leu Met Gly Tyr Ile Pro Leu Val
1 5

(2) INFORMATION FOR SEO ID NO: 164:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 43 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 164:

```
Tyr Gln Val Arg Asn Ser Thr Gly Leu Tyr His Val Thr Asn Asp Cys
1               5                  10                  15

Pro Asn Ser Ser Ile Val Tyr Glu Ala His Asp Ala Ile Leu His Thr
            20                  25                  30

Pro Gly Cys Val Pro Cys Val Arg Glu Gly Asn
        35                  40
```

(2) INFORMATION FOR SEO ID NO: 165:

(i) SEOUENCE CHARACTERISTICS:

(A) LENGTH: 42 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEOUENCE DESCRIPTION: SEQ ID NO: 165:

```
Gln Val Arg Asn Ser Thr Gly Leu Tyr His Val Thr Asn Asp Cys Pro
1               5                  10                  15

Asn Ser Ser Ile Val Tyr Glu Ala His Asp Ala Ile Leu His Thr Pro
            20                  25                  30

Gly Cys Val Pro Cys Val Arg Glu Gly Asn
        35                  40
```

(2) INFORMATION FOR SEO ID NO: 166:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: singla
(D) TOPOLOGY: -linear

(ii) MOLECULE TYPE: peptida

(xi) SEQUENCE DESCRIPTION: SEO ID NO: 166:

```
Lys Leu Val Ala Leu Gly Ile Asn Ala Val
1               5                  10
```

Claims

1. Usa of a polypeptide of about 8 to about 20 amino acids for the preparation of an HCV immunogenic composition, with said polypeptide comprising or consisting of about 8 to about 20 contiguous amino acids selected from the region comprised batween amino acid positions 157 to 176 of the core region of HCV: NH_2-$X_{30}X_{31}X_{32}DGX_{33}NX_{34}X_{35}TGNX_{36}PGCSFSI$-COOH (SEO ID NO 51), and with said contiguous amino acids containing a T-cell stimulating epitope, and wherain said polypeptide mimics tha T-cell immunological stimulation properties of the polypaptide as represented in SEO ID NO 13, and wherein X_{30} represents V or A or L, X_{31}

represents L or V or I, X_{32} represents E or G, X_{33} represents V or I, and X_{34} represents F or Y, X_{35} represents A or P, X_{36} represents L or I.

2. Use according to claim 1, for the preparation of an HCV immunogenic composition, with said polypeptide comprising or consisting of about 8 to about 20 contiguous emino acids selected from the region comprised between emino acid positions 157 to 176 of the core region of HCV:

VLEDGVNYATGNLPGCSFSI (SEQ ID NO 13 = peptide CORE 27) or
VLEDIVNYATGNLPGCSFSI (SEQ ID NO 73).

3. Use according to claim 1, for the preparation of an HCV immunogenic composition, with said polypeptide being chosen from the following list of peptides:

NH_2-$GX_{33}NX_{34}X_{35}TGNX_{36}$-COOH (SEQ ID NO 74),
NH_2-$X_{33}NX_{34}X_{35}TGNX_{36}$-COOH (SEQ ID NO 75),
NH_2-NX_{36}PGCSFSI-COOH (SEQ ID NO 76) and
NH_2-X_{36}PGCSFSI-COOH (SEQ ID NO 77).

4. Use according to claim 1, for the preparation of an HCV immunogenic composition, with said polypeptide being chosen from the following list of peptides:

GVNYATGNL (SEQ ID NO 78),
NLPGCSFSI (SEQ ID NO 80) and
LPGCSFSI (SEQ ID NO 81).

5. Use of a polypeptide of about 8 to about 20 amino ecids for the preparation of an HCV immunogenic composition, with said polypeptide comprising or consisting of about 8 to about 20 contiguous amino acids selected from the region comprised between amino acid positions 145 to 164 of the core region of HCV:
NH_2-$GGX_{25}X_{26}X_{27}X_{28}LX_{29}HGVRX_{30}X_{31}X_{32}DGX_{33}NX_{34}$-COOH (SEQ ID NO 52), and with said contiguous amino acids containing a T-cell stimulating epitope, and wherein said polypeptide mimics the T-cell immunological stimulation properties of the polypeptide es represented in SEQ ID NO 12, and wherein X_{25} represents A or V, X_{26} represents A or S, X_{27} represents R or A, X_{28} represents A or T or E, X_{29} represents A or E, X_{30} represents V or A or L, X_{31} represents L or V or I, X_{32} represents E or G, X_{33} represents V or I, and X_{34} represents F or Y.

6. Use according to claim 5, for the preparation of an HCV immunogenic composition, with said polypeptide comprising or consisting of about 8 to about 20 contiguous emino acids selected from the region comprised between amino acid positions 145 to 164 of the core region of HCV:

GGAARALAHGVRVLEDGVNY (SEQ ID ND 12 = peptide CORE 25) or
GGVAARALAHGVRVLEDGVNY (SEQ ID ND 118).

7. Use eccording to claim 5, for the preparation of an HCV immunogenic composition, with said polypeptide being chosen from the following list of peptides:

NH_2-$X_{28}LX_{29}HGVRX_{30}X_{31}$-COOH (SEQ ID NO 82),
NH_2-$LX_{29}HGVRX_{30}X_{31}$-COOH (SEQ ID NO 83),
NH_2-$GVRX_{30}X_{31}X_{32}DGX_{33}$-COOH (SEQ ID NO 84),
NH_2-$VRX_{30}X_{31}X_{32}DGX_{33}$-COOH (SEQ ID NO 85),
NH_2-$RX_{30}X_{31}X_{32}DGX_{33}NX_{34}$-COOH (SEQ ID NO 86), and
NH_2-$X_{30}X_{31}X_{32}DGX_{33}NX_{34}$-COOH (SEQ ID NO 87).

8. Use according to claim 5, for the preparation of an HCV immunogenic composition, with said polypeptide being chosen from the following list of peptides:

ALAHGVRVL (SEQ ID NO 88),
LAHGVRVL (SEQ ID NO 89),
VRVLEDGV (SEQ ID NO 90),

RVLEDGV (SEQ ID NO 91),
VLEDGVNY (SEQ ID NO 92), and
LEDGVNY (SEQ ID NO 93).

9. Use of a polypeptide of about 8 to about 20 emino ecids for the preparation of en HCV immunogenic composition, with said polypeptide comprising or consisting of about 8 to about 20 contiguous amino acids selected from the region comprised between amino acid positions 133 to 152 or the core region of HCV:
NH_2-$LX_{19}X_{20}YIPX_{21}X_{22}GX_{23}PX_{24}GGX_{25}X_{26}X_{27}X_{28}LX_{29}$ -COOH (SEQ ID NO 53), and with said contiguous amino acids conteining e T-cell stimulating epitope, and wherein said polypeptide mimics the T-cell immunological stimulation properties of the polypeptide as represented in SEQ ID NO 11, and wherein X_{19} represents M or I, X_{20} represents G or E, X_{21} represents L or V or I, X_{22} represents V or L, X_{23} represents A or G, X_{24} represents L, V or I, X_{25} represents A or V, X_{26} represents A or S, X_{27} represents R or A, X_{28} represents A or T or E, X_{29} represents A or E.

10. Use according to claim 9, for the preparation of an HCV immunogenic composition, with said polypeptide comprising or consisting of about 8 to about 20 contiguous amino acids selected from the region comprised between amino acid positions 133 to 152 of the core region of HCV: LMGYIPLVGAPLGGAARALA (SEQ ID NO 11 = peptide CORE 23).

11. Use according to claim 9, for the preparation of an HCV immunogenic composition, with said polypeptide being chosen from the following list of peptides:

NH_2-$LX_{19}X_{20}YIPX_{21}X_{22}GX_{23}PX_{24}GGX_{25}$-CODH (SEQ ID NO 62),
NH_2[-]-$X_{19}X_{20}YIPX_{21}X_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 63),
NH_2-$YIPX_{21}X_{22}GX_{23}PX_{24}$-COOH (SEQ ID NO 64),
NH_2-$IPX_{21}X_{22}GX_{23}PX_{24}$-COOH (SEQ ID ND 65),
NH_2-$X_{21}X_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 66)[-], and
NH_2-$X_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 68).

12. Use according to claim 9, for the preparation of an HCV immunogenic composition, with said polypeptide being

chosen from the following list of peptides:

LMGYIPLV (SEQ ID NO 69),

MGYIPLV (SEQ ID NO 70),
YIPLVGAPL (SEQ ID NO 71),
IPLVGAPL (SEQ ID NO 72),
LVGAPLGGA (SEQ ID NO 94), and
VGAPLGGA (SEQ ID NO 95).

13. Use of a polypeptide of about 8 to about 20 emino acids for the preparation of en HCV immunogenic composition, with said polypeptide comprising or consisting of about 8 to about 20 contiguous amino acids selected from the region comprised between amino acid positions 109 to 128 of the core region of HCV:
NH_2-$X_{11}X_{12}$DPR$X_{13}X_{14}$SRNX_{15}GX_{16}VIDTX_{17}TC -COOH (SEQ ID NO 54), and with said contiguous amino acids containing a T-cell stimulating epitope, and wherein said polypeptide mimics the T-cell immunological stimulation properties of the polypeptide as represented in SEO ID NO 9, and wherein X_{11} represents P or Q, X_{12} represents N or T, X_{13} represents R or H, X_{14} represents R or K, X_{15} represents L or V or F, X_{16} represents K or R, X_{17} represents L or I.

14. Use according to claim 13, for the preparation of an HCV immunogenic composition, with said polypeptide comprising or consisting of about 8 to ebout 20 contiguous amino acids selected from the region comprised between amino acid positions 109 to 128 of the core region of HCV: PTDPRRRSRNLGKVIDTLTC (SEQ ID NO 9 = peptide CORE 19).

15. Use according to claim 13, for the preparation of an HCV immunogenic composition, with said polypeptide being chosen from the following peptides:

NH_2-NX_{15}GX_{16}VIDTX_{17}-COOH (SEQ ID NO 96), and
NH_2-X_{15}GX_{16}VIDTX_{17}-COOH (SEQ ID NO 97).

16. Use according to claim 13, for the preparation of an HCV immunogenic composition, with said polypeptide being chosen from the following peptides:

NLGKVIDTL (SEQ ID NO 98), and
LGKVIDTL (SEQ ID NO 117).

17. Use of a polypeptide of about 8 to about 20 emino acids for the preparation of en HCV immunogenic composition, with said polypeptide comprising or consisting of et least 8 to about 20 contiguous emino acids selected from the region comprised between amino acid positions 73 to 92 of the core region of HCV:
NH_2-GX_1X_2WX_3X_4PGX_5PWPLYX_6NX_7GX_8G-COOH (SEQ ID NO 99), and with said contiguous amino acids containing a T-cell stimulating epitope, and wherein said polypeptide mimics the T-cell immunological stimulation properties of the polypeptide as represented in SEQ ID NO 6, and wherein X_1 represents R or K, X_2 represents A, S or T, X_3 represents A or G, X_4 represents Q, K or R, X_5 represents Y or H, X_6 represents G or A, X_7 represents E or K, end X_8 represents C, M or L.

18. Use according to claim 17, for the preparation of an HCV immunogenic composition, with seid polypeptide comprising or consisting of a least 8 to ebout 20 contiguous amino acids selected from the region comprised between emino ecid positions 73 to 92 of the core region of HCV:

GRTWAQPGYPWPLYGNEGCG (SEQ ID NO 6 = peptide CORE 13).

19. Use according to claim 17, for the preparation of an HCV immunogenic composition, with said polypeptide being selected from:

NH_2-$X_2WX_3X_4PGX_5PW$-COOH (SEQ ID NO 100) and
NH_2-$WX_3X_4PGX_5PW$-COOH (SEQ ID NO 101).

20. Use according to claim 17, for the preparation of an HCV immunogenic composition, with said polypeptide being selected from:

TWAQPGYPW (SEQ ID NO 102), and
WAQPGYPW (SEQ ID NO 103).

21. Use according to any of claims 1 to 20, wherein said T-cell stimulating epitope is a T-cell helper epitope.

22. Use according to any of claims 1 to 20, wherein said T-cell stimulating epitope is a CTL epitope.

23. Use according to any of claims 1 to 22, wherein said polypeptide is incorporated into a prophylactic vaccine composition.

24. Use according to any of claims 1 to 22, wherein said polypeptide is incorporated into a therapeutic vaccine composition.

25. A polypeptide consisting of multiple repeats, combinations or mimotopes of any of the contiguous amino acid sequences selected to contain a T-cell stimulating epitope[s] as defined in any of claims 1 to 22, with said combinations comprising two or more peptides joined into a single structure and with said mimotopes having one or more emino acid variations compared to said peptides as long as said mimotope peptides are capable of providing for immunological stimulation after which the T-cells are reactive with at least one strain of HCV.

26. Use according to any of claims 1 to 24, with said polypeptide being a recombinant polypeptide expressed by means of an expression vector comprising a nucleic acid insert encoding a polypeptide according to any of claims 1 to 22.

27. Use according to any of claims 1 to 24, wherein said polypeptide is operably linked to a pathogen related immunogen, such as the HCV envelope proteins E1 and E2, or the HCV NS3, NS4 or NS5 immunogens, or a HCV peptide containing a B cell stimulating epitope.

28. A peptide consisting of at least 8 contiguous amino acids of the sequence of any of the following peptides, with said peptides containing a T-cell epitope:

a)

NH_2-$X_{30}X_{31}X_{32}$DGX_{33}N$X_{34}X_{35}$TGN-X_{36}PGCSFSI-COOH (SEQ ID NO 51)
VLEDGVNYATGNLPGCSFSI (SEQ ID NO 13 = peptide CORE 27),
VLEDIVNYATGNLPGCSFSI (SEQ ID NO 73),
NH_2-GX_{33}N$X_{34}X_{35}$TGN-X_{36}-COOH (SEQ ID NO 74),
NH_2-X_{33}N$X_{34}X_{35}$TGN-X_{36}-COOH (SEQ ID NO 75),
NH_2-NX_{36}PGCSFSI-COOH (SEQ ID NO 76),

NH_2- X_{36}PGCSFSI-COOH (SEQ ID NO 77),
GVNYATGNL (SEQ ID NO 78), ~~or~~
NLPGCSFSI (SEQ ID NO 80), or
LPGCSFSI (SEQ ID NO 81),

wherein said peptide mimics the T-cell immunological stimulation properties of the peptide represented in SEQ ID NO 13;

b)

NH_2-GG$X_{25}X_{26}X_{27}X_{28}$LX_{29}HGVR$X_{30}X_{31}X_{32}$DGX_{33}NX_{34}-COOH (SEQ ID NO 52),
GGAARALAHGVRVLEDGVNY (SEQ ID NO 12 = peptide CORE 25),
GGVAARALAHGVRVLEDGVNY (SEQ ID NO 118),
NH_2-X_{28}LX_{29}HGVR$X_{30}X_{31}$-COOH (SEQ ID NO 82),
NH_2-LX_{29}HGVR$X_{30}X_{31}$-COOH (SEQ ID NO 83),
NH_2-GVR$X_{30}X_{31}X_{32}$DGX_{33}-COOH (SEQ ID NO 84),
NH_2-VR$X_{30}X_{31}X_{32}$DGX_{33}-COOH (SEQ ID NO 85),
NH_2-R$X_{30}X_{31}X_{32}$DGX_{33}NX_{34}-COOH (SEQ ID NO 86),
NH_2-$X_{30}X_{31}X_{32}$DGX_{33}NX_{34}-COOH (SEQ ID NO 87),
ALAHGVRVL (SEQ ID NO 88),
LAHGVRVL (SEQ ID NO 89),
VRVLEDGV (SEQ ID NO 90),
RVLEDGV (SEQ ID NO 91),
VLEDGVNY (SEQ ID NO 92), or
LEDGVNY (SEQ ID NO 93),

wherein said peptide mimics the T-cell immunological stimulation properties of the peptide represented in SEQ ID NO 12;

c)

NH_2-$LX_{19}X_{20}YIPX_{21}X_{22}GX_{23}PX_{24}GGX_{25}X_{26}X_{27}X_{28}LX_{29}$-COOH (SEQ ID NO 53),
LMGYIPLVGAPLGGAARALA (SEQ ID NO 11 = peptide CORE 23),
NH_2-$LX_{19}X_{20}YIPX_{21}X_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 62),
NH_2-$X_{19}X_{20}YIPX_{21}X_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 63),
NH_2-$YIPX_{21}X_{22}GX_{23}PX_{24}$-COOH (SEQ ID NO 64),
NH_2-$IPX_{21}X_{22}GX_{23}PX_{24}$-COOH (SEQ ID NO 65),
NH_2-$X_{21}X_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 66),

NH_2-$X_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 68),
LMGYIPLV (SEQ ID NO 69),
MGYIPLV (SEQ ID NO 70),
YIPLVGAPL (SEQ ID NO 71),
IPLVGAPL (SEQ ID NO 72), [~~or~~]
LVGAPLGGA (SEQ ID NO 94), or
VGAPLGGA (SEQ ID NO 95),

wherein said peptide mimics the T-cell immunological stimulation properties of the peptide represented in SEQ ID NO 11;

d)

NH_2-$X_{11}X_{12}DPRX_{13}X_{14}SRNX_{15}GX_{16}VIDTX_{17}TC$ -COOH (SEQ ID NO 54),
PTDPRRRSRNLGKVIDTLTC (SEQ ID NO 9 = peptide CORE 19),
NH_2-$NX_{15}GX_{16}VIDTX_{17}$-COOH (SEQ ID NO 96),
NH_2-$X_{15}GX_{16}VIDTX_{17}$-COOH (SEQ ID NO 97), [~~or~~]
NLGKVIDTL (SEQ ID NO 98), or
LGKVIDTL (SEQ ID NO 117),

wherein said peptide mimics the T-cell immunological stimulation properties of the peptide as represented in SEQ ID NO 9;

e)

NH_2-$GX_1X_2WX_3X_4PGX_5PWPLYX_8NX_7GX_8G$-COOH (SEQ ID NO 99),
GRTWAQPGYPWPLYGNEGCG (SEQ ID NO 6 = peptide CORE 13),
NH_2-$X_2WX_3X_4PGX_5PW$-COOH (SEQ ID NO 100),
NH_2-$WX_3X_4PGX_5PW$-COOH (SEQ ID NO 101), [~~or~~]
TWAQPGYPW (SEQ ID NO 102), or
WAQPGYPW (SEQ ID NO 103),

wherein said peptide mimics the T-cell immunological stimulation properties of the peptide as represented in SEQ ID NO 6;
wherein X_1 represents R or K, X_2 represents A, S or T, X_3 represents A or G, X_4 represents Q, K or R, X_5 represents Y or H, X_6 represents G or A, X_7 represents E or K, X_8 represents C, M or L, X_9 represents W or L, X_{10} represents S, N, T, D or H, X_{11} represents P or Q, X_{12} represents N or T, X_{13} represents R or H, X_{14} represents R or K, X_{15} represents L or V or F, X_{16} represents K or R, X_{17} represents L or I, X_{18} represents F or L, X_{19} represents M or I, X_{20} represents G or E, X_{21} represents L or V or I, X_{22} represents V or L, X_{23} represents A or G, X_{24} represents L, V or I, X_{25} represents A or V, X_{26} represents A or S, X_{27} represents R or A, X_{28} represents A or T or E, X_{29} represents A or E, X_{30} represents V or A or L, X_{31} represents L or V or I, X_{32} represents E or G, X_{33} represents V or I, X_{34} represents F or Y, X_{35} represents A or P, and X_{36} represents L or I.

29. An immunogenic composition consisting of or comprising at least one of the peptides or polypeptides according to claim 28 mixed with a pharmaceutically acceptable excipient.

30. A vaccine composition according to claim 29.

31. A prophylactic vaccine composition according to claim 30.

32. A therapeutic vaccine composition according to claim 30.

33. A composition according to any of claims 29 to 32, with said composition comprising in addition to any of the polypeptides according to claim 28, a peptide or polypeptide containing et least one B cell stimulating epitope of HCV, and/or a structural HCV polypeptide, and/or a non-structural HCV polypeptide.

34. A composition according to any of claims 29 to 33, wherein said polypeptide according to claim 28 is mixed with HBsAg or HBcAg particles, HBV immunogens, HIV immunogens and/or HTLV immunogens.

35. Use of a recombinant expression vector comprising a nucleic acid insert encoding a polypeptide as defined in any of claims 1 to 22[24] for the preparetion of a HCV immunogenic composition.

Patentansprüche

1. Verwendung eines Polypeptids aus etwa 8 bis etwa 20 Aminosäuren zur Herstellung einer HCV-immunogenen Zusammensetzung, wobei das Polypeptid etwa 8 bis etwa 20 aufeinanderfolgende Aminosäuren, ausgewählt aus dem von den Aminosäurepositionen 157 bis 176 des HCV-Kernbereichs umfeßten Bereich:
NH_2-$X_{30}X_{31}X_{32}DGX_{33}NX_{34}X_{35}TGNX_{36}PGCSFSI$-CODH (SEQ ID NO 51), umfaßt bzw. aus diesen besteht und wobei die eufeinanderfolgenden Aminosäuren ein T-Zellen stimulierendes Epitop enthalten, und worin das Polypeptid die Charakteristik des wie in SEQ ID NO 13 dargestellten Polypeptids, T-Zellen immunologisch zu stimulieren, imitiert, und worin X_{30} für V oder A oder L, X_{31} für L oder V oder I, X_{32} für E oder G, X_{33} für V oder I, X_{34} für F oder Y, X_{35} für A oder P und X_{36} für L oder I steht.

2. Verwendung nach Anspruch 1 zur Herstellung einer HCV-immunogenen Zusammensetzung, wobei das Polypeptid etwa 8 bis etwa 20 aufeinanderfolgende Aminosäuren, ausgewählt aus dem von den Aminosäurepositionen 157 bis 176 des HCV-Kernbereichs umfaßten Bereich:

VLEDGVNYATGNLPGCSFSI (SEO ID NO 13 = Peptid CORE 27) oder
VLEDIVNYATGNLPGCSFSI (SEO ID NO 73), umfaßt bzw. aus diesen besteht.

3. Verwendung nach Anspruch 1 zur Herstellung einer HCV-immunogenen Zusammensetzung, wobei das Polypeptid von der folgenden Liste von Peptiden gewählt wird:

NH_2-$GX_{33}NX_{34}X_{35}TGNX_{36}$-COOH (SEQ ID NO 74),
NH_2-$X_{33}NX_{34}X_{35}TGNX_{36}$-COOH (SEQ ID NO 75),
NH_2-NX_{36}PGCSFSI-COOH (SEQ ID NO 76) und
NH_2-X_{36}PGCSFSI-COOH (SEQ ID NO 77).

4. Verwendung nach Anspruch 1 zur Herstellung einer HCV-immunogenen Zusammensetzung, wobei das Polypeptid von der folgenden Liste von Peptiden gewählt wird:

GVNYATGNL (SEQ ID NO 78),
NLPGCSFSI (SEQ ID NO 80) und
LPGCSFSI (SEQ ID NO 81).

5. Verwendung eines Polypeptids aus etwe 8 bis etwa 20 Aminosäuren zur Herstellung einer HCV-immunogenen Zusammensetzung, wobei das Polypeptid etwa 8 bis etwa 20 aufeinanderfolgende Aminosäuren, ausgewählt aus dem von den Aminosäurepositionen 145 bis 164 des HCV-Kembereichs umfaßten Bereich:
NH_2-$GGX_{25}X_{26}X_{27}X_{28}LX_{29}HGVRX_{30}X_{31}X_{32}DGX_{33}NX_{34}$-COOH (SEO ID NO 52), umfaßt bzw. aus diesen besteht und wobei die aufeinanderfolgenden Aminosäuren ein T-Zellen stimulierendes Epitop enthalten, und worin das Polypeptid die Charakteristik des wie in SEO ID NO 12 dargestellten Polypeptids, T-Zellen immunologisch zu stimulieren, imitiert, und worin X_{25} für A oder V, X_{26} für A oder S, X_{27} für R oder A, X_{28} für A oder T oder E, X_{29} für A oder E, X_{30} für V oder A oder L, X_{31} für L oder V oder I, X_{32} für E oder G, X_{33} für V oder I und X_{34} für F oder Y steht.

6. Verwendung nach Anspruch 5 zur Herstellung einer HCV-immunogenen Zusammensetzung, wobei das Polypeptid etwa 8 bis etwa 20 aufeinanderfolgende Aminosäuren, eusgewählt aus dem von den Aminosäurepositionen 145 bis 164 des HCV-Kernbereichs umfaßten Bereich:
GGAARALAHGVRVLEDGVNY (SEO ID NO 12 = Peptid CDRE 25) oder
GGVAARALAHGVRVLEDGVNY (SEO ID NO 118), umfaßt bzw. aus diesen besteht.

7. Verwendung nach Anspruch 5 zur Herstellung einer HCV-immunogenen Zusammensetzung, wobei das Polypeptid von der folgenden Liste von Peptiden gewählt wird:

NH_2-$X_{28}LX_{29}HGVRX_{30}X_{31}$-COOH (SEQ ID NO 82),
NH_2-$LX_{29}HGVRX_{30}X_{31}$-COOH (SEQ ID NO 83),
NH_2-$GVRX_{30}X_{31}X_{32}DGX_{33}$-COOH (SEQ ID NO 84),
NH_2-$VRX_{30}X_{31}X_{32}DGX_{33}$-COOH (SEQ ID NO 85),
NH_2-$RX_{30}X_{31}X_{32}DGX_{33}NX_{34}$-COOH (SEQ ID NO 86) und
NH_2-$X_{30}X_{31}X_{32}DGX_{33}NX_{34}$-COOH (SEQ ID NO 87).

8. Verwendung nach Anspruch 5 zur Herstellung einer HCV-immunogenen Zusemmensetzung, wobei das Polypeptid von der folgenden Liste von Peptiden gewählt wird:

ALAHGVRVL (SEQ ID NO 88),
LAHGVRVL (SEQ ID NO 89),
VRVLEDGV (SEQ ID NO 90),
RVLEDGV (SEQ ID NO 91),
VLEDGVNY (SEQ ID NO 92) und
LEDGVNY (SEQ ID NO 93).

9. Verwendung eines Polypeptids aus etwa 8 bis etwa 20 Aminosäuren zur Herstellung einer HCV-immunogenen Zusammensetzung, wobei das Polypeptid etwa 8 bis etwa 20 aufeinanderfolgende Aminosäuren, ausgewählt aus dem von den Aminosäurepositionen 133 bis 152 des HCV-Kernbereichs umfaßten Bereich:
NH_2-$LX_{19}X_{20}YIPX_{21}X_{22}GX_{23}PX_{24}GGX_{25}X_{26}X_{27}X_{28}LX_{29}$-COOH (SEQ ID NO 53), umfaßt bzw. aus diesen besteht und wobei die aufeinanderfolgenden Aminosäuren ein T-Zellen stimulierendes Epitop enthalten, und worin das Polypeptid die Charakteristik des wie in SEQ ID NO 11 dargestellten Polypeptids, T-Zellen immunologisch zu stimulieren, imitiert, und worin X_{19} für M oder I, X_{20} für G oder E, X_{21} für L oder V oder I, X_{22} für V oder L, X_{23} für A oder G, X_{24} für L, V oder I, X_{25} für A oder V, X_{26} für A oder S, X_{27} für R oder A, X_{28} für A oder T oder E und X_{29} für A oder E steht.

10. Verwendung nach Anspruch 9 zur Herstellung einer HCV-immunogenen Zusammensetzung, wobei das Polypeptid etwa 8 bis etwa 20 aufeinanderfolgende Aminosäuren, ausgewählt aus dem von den Aminosäurepositionen 133 bis 152 des HCV-Kernbereichs umfaßten Bereich:
LMGYIPLVGAPLGGAARALA (SEO ID NO 11 = Peptid CORE 23), umfaßt bzw. aus diesen besteht.

11. Verwendung nach Anspruch 9 zur Herstellung einer HCV-immunogenen Zusammensetzung, wobei das Polypeptid von der folgenden Liste von Peptiden gewählt wird:

NH_2-$LX_{19}X_{20}YIPX_{21}X_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 62),
NH_2-$X_{19}X_{20}YIPX_{21}X_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 63),
NH_2-$YIPX_{21}X_{22}GX_{23}PX_{24}$-COOH (SEQ ID NO 64),
NH_2-$IPX_{21}X_{22}GX_{23}PX_{24}$-COOH (SEQ ID NO 65),
NH_2-$X_{21}X_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 66) und
NH_2-$X_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 68).

12. Verwendung nach Anspruch 9 zur Herstellung einer HCV-immunogenen Zusammensetzung, wobei das Polypeptid von der folgenden Liste von Peptiden gewählt wird:

LMGYIPLV (SEQ ID NO 69),
MGYIPLV (SEQ ID NO 70),
YIPLVGAPL (SEQ ID NO 71),
IPLVGAPL (SEQ ID NO 72),
LVGAPLGGA (SEQ ID NO 94) und
VGAPLGGA (SEQ ID NO 95).

13. Verwendung eines Polypeptids aus etwa 8 bis etwa 20 Aminosäuren zur Herstellung einer HCV-immunogenen Zusammensetzung, wobei das Polypeptid etwa 8 bis etwa 20 aufeinanderfolgende Aminosäuren, ausgewählt aus dem von den Aminosäurepositionen 109 bis 128 des HCV-Kernbereichs umfaßten Bereich:
NH_2-$X_{11}X_{12}DPRX_{13}X_{14}SRNX_{15}GX_{16}VIDTX_{17}TC$-COOH (SEO ID NO 54), umfaßt bzw. aus diesen besteht und

wobei die aufeinanderfolgenden Aminosäuren ein T-Zellen stimulierendes Epitop enthalten, und worin das Polypeptid die Charakteristik des wie in SEO ID NO 9 dargestellten Polypeptids, T-Zellen immunologisch zu stimulieren, imitiert, und worin X_{11} für P oder O, X_{12} für N oder T, X_{13} für R oder H, X_{14} für R oder K, X_{15} für L oder V oder F, X_{16} für K oder R und X_{17} für L oder I steht.

14. Verwendung nach Anspruch 13 zur Herstellung einer HCV-immunogenen Zusammensetzung, wobei das Polypeptid etwa 8 bis etwa 20 aufeinanderfolgende Aminosäuren, ausgewählt aus dem von den Aminosäurepositionen 109 bis 128 des HCV-Kernbereichs umfaßten Bereich: PTDPRRRSRNLGKVIDTLTC (SEO ID NO 9 = Peptid CORE 19), umfaßt bzw. aus diesen besteht.

15. Verwendung nach Anspruch 13 zur Herstellung einer HCV-immunogenen Zusammensetzung, wobei das Polypeptid von den folgenden Peptiden gewählt wird:

NH_2-$NX_{15}GX_{16}$VIDTX_{17}-COOH (SEQ ID NO 96) und
NH_2-$X_{15}GX_{16}$VIDTX_{17}-COOH (SEQ ID NO 97).

16. Verwendung nach Anspruch 13 zur Herstellung einer HCV-immunogenen Zusammensetzung, wobei das Polypeptid von den folgenden Peptiden gewählt wird:

NLGKVIDTL (SEQ ID NO 98) und
LGKVIDTL (SEQ ID NO 117).

17. Verwendung eines Polypeptids aus etwa 8 bis etwa 20 Aminosäuren zur Herstellung einer HCV-immunogenen Zusammensetzung, wobei das Polypeptid mindestens 8 bis etwe 20 aufeinanderfolgende Aminosäuren, ausgewählt aus dem von den Aminosäurepositionen 73 bis 92 des HCV-Kernbereichs umfaßten Bereich: NH_2-$GX_1X_2WX_3X_4PGX_5PWPLYX_6NX_7GX_8$G-COOH (SEO ID NO 99), umfaßt bzw. aus diesen besteht und wobei die aufeinanderfolgenden Aminosäuren ein T-Zellen stimulierendes Epitop enthalten, und worin das Polypeptid die Charakteristik des wie in SEO ID NO 6 dargestellten Polypeptids, T-Zellen immunologisch zu stimulieren, imitiert, und worin X_1 für R oder K, X_2 für A, S oder T, X_3 für A oder G, X_4 für O, K oder R, X_5 für Y oder H, X_6 für G oder A, X_7 für E oder K und X_8 für C, M oder L steht.

18. Verwendung nach Anspruch 17 zur Herstellung einer HCV-immunogenen Zusammensetzung, wobei das Polypeptid mindestens 8 bis etwa 20 aufeinanderfolgende Aminosäuren, ausgewählt aus dem von den Aminosäurepositionen 73 bis 92 des HCV-Kernbereichs umfaßten Bereich:

GRTWAQPGYPWPLYGNEGCG (SEQ ID NO 6 = Peptid CORE 13),

umfaßt bzw. aus diesen besteht.

19. Verwendung nach Anspruch 17 zur Herstellung einer HCV-immunogenen Zusammensetzung, wobei das Polypeptid ausgewählt wird aus:

NH_2-$X_2WX_3X_4PGX_5$PW-COOH (SEQ ID NO 100) und
NH_2-$WX_3X_4PGX_5$PW-COOH (SEQ ID NO 101).

20. Verwendung nach Anspruch 17 zur Herstellung einer HCV-immunogenen Zusammensetzung, wobei das

Polypeptid ausgewählt wird aus:
TWAQPGYPW (SEQ ID NO 102) und
WAQPGYPW (SEQ ID NO 103).

21. Verwendung nach einem der Ansprüche 1 bis 20, wobei es sich bei dem T-Zellen stimulierenden Epitop um ein T-Zellen-Helferepitop handelt.

22. Verwendung nach einem der Ansprüche 1 bis 20, wobei es sich bei dem T-Zellen stimulierenden Epitop um ein CTL-Epitop handelt.

23. Verwendung nach einem der Ansprüche 1 bis 22, wobei das Polypeptid in eine prophylaktische Impfstoffzusammensetzung integriert wird.

24. Verwendung nach einem der Ansprüche 1 bis 22, wobei das Polypeptid in eine therapeutische Impfstoffzusammensetzung integriert wird.

25. Polypeptid, bestehend aus mehrfachen Wiederholungen, Kombinationen oder Mimotopen einer beliebigen der aufgrund der in ihnen enthaltenen, eine T-Zelle stimulierenden Epitope gemäß einem der Ansprüche 1 bis 22 eusgewählten Sequenzen aus aufeinanderfolgenden Aminosäuren, wobei die Kombinationen zwei oder mehrere, zu einer einzigen Struktur verbundene Peptide umfassen und wobei die Mimotope verglichen mit den Peptiden eine oder mehrere Aminosäurevariationen aufweisen können, solange die mimotopischen Peptide in der Lage sind, für eine immunologische Stimulierung zu sorgen, wonach die T-Zellen auf wenigstens einen HCV-Stamm reagieren.

26. Verwendung nach einem der Ansprüche 1 bis 24, wobei es sich bei dem Polypeptid um ein rekombinantes Polypeptid handelt, das mittels eines eine für ein Polypeptid nach einem der Ansprüche 1 bis 22 codierende Nukleinsäureinsertion enthaltenden Expressionsvektors exprimiert wird.

27. Verwendung nach einem der Ansprüche 1 bis 24, wobei das Polypeptid mit einem mit einem Krankheitserreger in Zusammenhang stehenden Immunogen, wie z.B. den HCV-Hüllproteinen E1 und E2 oder den HCV-Immunogenen NS3, NS4 und NS5 oder einem ein B-Zellen stimulierendes Epitop enthaltenden HCV-Peptid, operativ verknüpft ist.

28. Peptid, bestehend eus mindestens 8 aufeinanderfolgenden Aminosäuren der Sequenz eines beliebigen der folgenden Peptide, wobei die Peptide ein T-Zellen-Epitop enthalten:

a)

NH_2-$X_{30}X_{31}X_{32}$DGX_{33}N$X_{34}X_{35}$TGNX_{36}PGCSFSI-COOH (SEQ ID NO 51),
VLEDGVNYATGNLPGCSFSI (SEQ ID NO 13 = Peptid CORE 27),
VLEDIVNYATGNLPGCSFSI (SEQ ID NO 73),
NH_2-GX_{33}N$X_{34}X_{35}$TGNX_{36}-COOH (SEQ ID NO 74),
NH_2-X_{33}N$X_{34}X_{35}$TGNX_{36}-COOH (SEQ ID NO 75),
NH_2-NX_{36}PGCSFSI-COOH (SEQ ID NO 76),
NH_2-X_{36}PGCSFSI-COOH (SEQ ID NO 77),
GVNYATGNL (SEQ ID NO 78),
NLPGCSFSI (SEQ ID NO 80) oder
LPGCSFSI (SEQ ID NO 81),

worin das Peptid die Charakteristik des wie in SEQ ID NO 13 dargestellten Peptids, T-Zellen immunologisch zu stimulieren, imitiert;
b)

NH_2-GG$X_{25}X_{26}X_{27}X_{28}$LX_{29}HGVR$X_{30}X_{31}X_{32}$DGX_{33}NX_{34}-COOH (SEQ ID NO 52),
GGAARALAHGVRVLEDGVNY (SEQ ID NO 12 = Peptid CORE 25),
GGVAARALAHGVRVLEDGVNY (SEQ ID NO 118),
NH_2-X_{28}LX_{29}HGVR$X_{30}X_{31}$-COOH (SEQ ID NO 82),
NH_2-LX_{29}HGVR$X_{30}X_{31}$-COOH (SEQ ID NO 83),
NH_2-GVR$X_{30}X_{31}X_{32}$DGX_{33}-COOH (SEQ ID NO 84),
NH_2-VR$X_{30}X_{31}X_{32}$DGX_{33}-COOH (SEQ ID NO 85),
NH_2-R$X_{30}X_{31}X_{32}$DGX_{33}NX_{34}-COOH (SEQ ID NO 86),
NH_2-$X_{30}X_{31}X_{32}$DGX_{33}NX_{34}-COOH (SEQ ID NO 87),
ALAHGVRVL (SEQ ID NO 88),
LAHGVRVL (SEQ ID NO 89),
VRVLEDGV (SEQ ID NO 90),
RVLEDGV (SEQ ID NO 91),
VLEDGVNY (SEQ ID NO 92) oder

LEDGVNY (SEQ ID NO 93),

worin das Peptid die Charakteristik des wie in SEQ ID NO 12 dargestellten Peptids, T-Zellen immunologisch zu stimulieren, imitiert;
c)

NH_2-$LX_{19}X_{20}YIPX_{21}X_{22}GX_{23}PX_{24}GGX_{25}X_{26}X_{27}X_{28}LX_{29}$-COOH (SEQ ID NO 53),

LMGYIPLVGAPLGGAARALA (SEQ ID NO 11 = Peptid CORE 23),

NH_2-$LX_{19}X_{20}YIPX_{21}X_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 62),

NH_2-$X_{19}X_{20}YIPX_{21}X_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 63),

NH_2-$YIPX_{21}X_{22}GX_{23}PX_{24}$-COOH (SEQ ID NO 64),

NH_2-$IPX_{21}X_{22}GX_{23}PX_{24}$-COOH (SEQ ID NO 65),

NH_2-$X_{21}X_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 66),

NH_2-$X_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 68),

LMGYIPLV (SEQ ID NO 69),

MGYIPLV (SEQ ID NO 70),

YIPLVGAPL (SEQ ID NO 71),

IPLVGAPL (SEQ ID NO 72),

LVGAPLGGA (SEQ ID NO 94) or

VGAPLGGA (SEQ ID NO 95),

worin das Peptid die Charakteristik des wie in SEQ ID NO 11 dargestellten Peptids, T-Zellen immunologisch zu stimulieren, imitiert;

d)

NH_2-$X_{11}X_{12}DPRX_{13}X_{14}SRNX_{15}GX_{16}VIDTX_{17}TC$-COOH (SEQ ID NO 54),

PTDPRRRSRNLGKVIDTLTC (SEQ ID NO 9 = Peptid CORE 19),

NH_2-$NX_{15}GX_{16}VIDTX_{17}$-COOH (SEQ ID NO 96),

NH_2-$X_{15}GX_{16}VIDTX_{17}$-COOH (SEQ ID NO 97),

NLGKVIDTL (SEQ ID NO 98) oder

LGKVIDTL (SEQ ID NO 117),

worin das Peptid die Charekteristik des wie in SEQ ID NQ 9 dargestellten Peptids, T-Zellen immunologisch zu stimulieren, imitiert;

e)

NH_2-$GX_1X_2WX_3X_4PGX_5PWPLYX_6NX_7GX_8G$-COOH (SEQ ID NO 99),

GRTWAQPGYPWPLYGNEGCG (SEQ ID NO 6 = Peptid CORE 13),

NH_2-$X_2WX_3X_4PGX_5PW$-COOH (SEQ ID NO 100),

NH_2-$WX_3X_4PGX_5PW$-COOH (SEQ ID NO 101),

TWAQPGYPW (SEQ ID NO 102) oder

WAQPGYPW (SEQ ID NO 103),

worin das Peptid die Charakteristik des wie in SEQ ID NO 6 dargestellten Peptids, T-Zellen immunologisch

zu stimulieren, imitiert;
worin X_1 für R oder K, X_2 für A, S oder T, X_3 für A oder G, X_4 für Q, K oder R, X_5 für Y oder H, X_6 für G oder A, X_7 für E oder K, X_8 für C, M oder L, X_9 für W oder L, X_{10} für S, N, T, D oder H, X_{11} für P oder Q, X_{12} für N oder T, X_{13} für R oder H, X_{14} für R oder K, X_{15} für L oder V oder F, X_{16} für K oder R, X_{17} für L oder I, X_{18} für F oder L, X_{19} für M oder I, X_{20} für G oder E, X_{21} für L oder V oder I, X_{22} für V oder L, X_{23} für A oder G, X_{24} für L, V oder I, X_{25} für A oder V, X_{26} für A oder S, X_{27} für R oder A, X_{28} für A oder T oder E, X_{29} für A oder E, X_{30} für V oder A oder L, X_{31} für L oder V oder I, X_{32} für E oder G, X_{33} für V oder I, X_{34} für F oder Y, X_{35} für A oder P und X_{36} für L oder I steht.

29. Immunogene Zusammensetzung, bestehend aus bzw. umfassend wenigstens ein mit einem pharmazeutisch unbedenklichen Hilfsstoff vermischtes Peptid oder Polypeptid nach Anspruch 28.

30. Impfstoffzusammensetzung nach Anspruch 29.

31. Prophylaktische Impfstoffzusammensetzung nach Anspruch 30.

32. Therapeutische Impfstoffzusammensetzung nach Anspruch 30.

33. Zusammensetzung nach einem der Ansprüche 29 bis 32, wobei die Zusammensetzung neben einem beliebigen der Polypeptide nach Anspruch 28 ein Peptid oder Polypeptid, das wenigstens ein B-Zellen stimulierendes HCV-Epitop enthält, und/oder ein HCV-Strukturpolypeptid und/oder ein nicht strukturelles HCV-Polypeptid umfaßt.

34. Zusammensetzung nach einem der Ansprüche 29 bis 33, worin das Polypeptid nach Anspruch 28 in mit HBsAgoder HBcAg-Partikeln, HBV-Immunogenen, HIV-Immunogenen und/oder HTLV-Immunogenen vermischter Form vorliegt.

35. Verwendung eines rekombinanten Expressionsvektors, der eine für ein Polypeptid gemäß einem der Ansprüche 1 bis 22 codierende Nukleinsäureinsertion enthält, zur Herstellung einer HCV-immunogenen Zusammensetzung.

Revendications

1. Utilisation d'un polypeptide d'environ 8 à environ 20 acides aminés pour la préparation d'une composition immunogène de HCV, ledit polypeptide comprenant ou contenant d'environ 8 à environ 20 acides aminés contigus sélectionnés à partir de la région comprise entre les positions d'acides eminés 157 à 176 de la région de noyau de HCV :

$$NH_2\text{-}X_{30}X_{31}X_{32}DGX_{33}NX_{34}X_{35}TGNX_{36}PGCSFSI\text{-}COOH \quad (SEQ\ ID\ NO\ 51),$$

et lesdits acides aminés contigus contenant un épitope stimulant des lymphocytes T, et dans laquelle ledit polypeptide mime les propriétés de stimulation immunologique des lymphocytes T du polypeptide tel que représenté à la SEQ ID NO 13, et dans laquelle X_{30} représente V ou A ou L, X_{31} représente L ou V ou I, X_{32} représente E ou G, X_{33} représente V ou I, et X_{34} représente F ou Y, X_{35} représente A ou P, X_{36} représente L ou I.

2. Utilisation suivant la revendication 1, pour la préparation d'une composition immunogène de HCV, ledit polypeptide comprenant ou contenant d'environ 8 à environ 20 acides aminés contigus sélectionnés à partir de la région comprise entre les positions d'acides aminés 157 à 176 de le région de noyau de HCV:

VLEDGVNYATGNLPGCSFSI (SEQ ID NO 13 = peptide CORE 27)
ou VLEDIVNYATGNLPGCSFSI (SEQ ID NO 73).

3. Utilisation suivant la revendicetion 1, pour la préparation d'une composition immunogène de HCV, ledit polypeptide étent choisi parmi la liste suivante de peptides :

NH_2-$GX_{33}NX_{34}X_{35}TGNX_{36}$-COOH (SEQ ID NO 74),

NH_2-$X_{33}NX_{34}X_{35}TGNX_{36}$-COOH (SEQ ID NO 75),

NH_2-NX_{36}PGCSFSI-COOH (SEQ ID NO 76), et

NH_2-X_{36}PGCSFSI-COOH (SEQ ID NO 77).

4. Utilisation suivant la revendication 1, pour la préparation d'une composition Immunogéne de HCV, ledit polypeptide étant choisi parmi la liste suivante de peptides :

GVNYATGNL (SEQ ID NO 78)

NLPGCSFSI (SEQ ID NO 80) et

LPGCSFSI (SEQ ID NO 81).

5. Utilisation d'un polypeptide d'environ 8 à environ 20 acides aminés pour la préparation d'une composition immunogéne de HCV, ledit polypeptide comprenant ou contenant d'environ 8 à environ 20 acides aminés contigus sélectionnés parmi la région comprise entre les positions d'acides aminés 145 à 164 de la région de noyau de HCV : NH_2-$GGX_{25}X_{26}X_{27}X_{28}LX_{29}HGVRX_{30}X_{31}X_{32}DGX_{33}NX_{34}$-COOH (SEQ ID NO 52), et lesdits acides aminés contigus contenant un épitope de stimulant des lymphocytes T, dans laquelle ledit polypeptide mime les propriétés de stimulation immunologique de lymphocytes T du polypeptide tel que représenté à la SEQ ID NO 12, et dans laquelle X_{25} représente A ou V, X_{26} représente A ou S, X_{27} représente R ou A, X_{28} représente A ou T ou E, X_{29} représente A ou E, X_{30} représente V ou A ou L, X_{31} représente L ou V ou I, X_{32} représente E ou G, X_{33} représente V ou I, et X_{34} représente F ou Y.

6. Utilisation suivant la revendication 5, pour la préparation d'une composition immunogéne de HCV, ledit polypeptide comprenant ou contenant d'environ 8 à environ 20 acides aminés contigus sélectionnés parmi la région comprise entre les positions d'acides aminés 145 à 164 de la région de noyau de HCV :

GGAARALAHGVRVLEDGVNY (SEQ ID NO 12 = peptide CORE 25)

ou GGVAARALAHGVRVLEDGVNY (SEQ ID NO 118).

7. Utilisation suivant la revendication 5, pour la préparation d'une composition immunogéne de HCV, ledit polypeptide étant choisi parmi la liste suivante de peptides :

NH_2-$X_{28}LX_{29}HGVRX_{30}X_{31}$-COOH (SEQ ID NO 82),

NH_2-$LX_{29}HGVRX_{30}X_{31}$-COOH (SEQ ID NO 83),

NH_2-$GVRX_{30}X_{31}X_{32}DGX_{33}$-COOH (SEQ ID NO 84),

NH_2-$VRX_{30}X_{31}X_{32}DGX_{33}$-COOH (SEQ ID NO 85),

NH_2-$RX_{30}X_{31}X_{32}DGX_{33}NX_{34}$-COOH (SEQ ID NO 86), et

NH_2-$X_{30}X_{31}X_{32}DGX_{33}NX_{34}$-COOH (SEQ ID NO 87).

8. Utilisation suivant la revendication 5, pour la préparation d'une composition immunogène de HCV, ledit polypeptide étant choisi parmi la liste suivante de peptides :

ALAHGVRVL (SEQ ID NO 88),

LAHGVRVL (SEQ ID NO 89),

VRVLEDGV (SEQ ID NO 90),

RVLEDGV (SEQ ID NO 91),

VLEDGVNY (SEQ ID NO 92), et

LEDGVNY (SEQ ID NO 93).

9. Utilisation d'un polypeptide d'environ 8 à environ 20 acides aminés pour la préparation d'une composition immunogène de HCV, ledit polypeptide comprenant ou contenant d'environ 8 à environ 20 acides aminés contigus sélectionnés parmi la région comprise entre les positions d'acides aminés 133 à 152 ou la région de noyau de HCV : NH_2-L$X_{19}X_{20}$YIP$X_{21}X_{22}$GX_{23}PX_{24}GG$X_{25}X_{26}X_{27}X_{28}$LX_{29}-COOH (SEQ ID NO 53), et lesdits acides aminés contigus contenant un épitope stimulant des lymphocytes T, et dans laquelle ledit polypeptide mime les propriétés de stimulation de lymphocytes T du polypeptide tel que représenté à la SEQ ID NO 11 et dans laquelle X_{19} représente M ou I, X_{20} représente G ou E, X_{21} représente L ou V ou I, X_{22} représente V ou L, X_{23} représente A ou G, X_{24} représente L, V ou I, X_{25} représente A ou V, X_{26} représente A ou S, X_{27} représente R ou A, X_{28} représente A ou T ou E, X_{29} représente A ou E.

10. Utilisation suivant la revendication 9, pour la préparation d'une composition immunogène de HCV, ledit polypeptide comprenant ou contenant d'environ 8 é environ 20 acides aminés contigus sélectionnés parmi la région comprise entre les positions d'acides aminés 133 à 152 de la région de noyau de HCV :

LMGYIPLVGAPLGGAARALA (SEQ ID NO 11 = peptide CORE 23).

11. Utilisation suivant la revendication 9, pour la préparation d'une composition immunogène de HCV, ledit polypeptide étant choisi parmi la liste suivante de peptides :

NH_2-L$X_{19}X_{20}$YIP$X_{21}X_{22}$GX_{23}PX_{24}GGX_{25}-COOH (SEQ ID NO 62),

NH_2-$X_{19}X_{20}$YIP$X_{21}X_{22}$GX_{23}PX_{24}GGX_{25}-COOH (SEQ ID NO 63),

NH_2-YIP$X_{21}X_{22}$GX_{23}PX_{24}-COOH (SEQ ID NO 64),

NH_2-IP$X_{21}X_{22}$GX_{23}PX_{24}-COOH (SEQ ID NO 65),

NH_2-$X_{21}X_{22}$GX_{23}PX_{24}GGX_{25}-COOH (SEQ ID NO 66), et

NH_2-X_{22}GX_{23}PX_{24}GGX_{25}-COOH (SEQ ID NO 68).

12. Utilisation suivant la revendication 9, pour la préparation d'une composition immunogène de HCV, ledit polypeptide étant choisi parmi la liste suivante de peptides :

LMGYIPLV (SEQ ID NO 69),

MGYIPLV (SEQ ID NO 70),

YIPLVGAPL (SEQ ID NO 71),

IPLVGAPL (SEQ ID NO 72),

LVGAPLGGA (SEQ ID NO 94), et

VGAPLGGA (SEQ ID NO 95).

13. Utilisation d'un polypeptide d'environ 8 à environ 20 acides aminés pour la préparation d'une composition immunogéne de HCV, ledit polypeptide comprenant ou contenant d'environ 8 é environ 20 acides aminés contigus sélectionnés parmi la région comprise entre les positions d'acides aminés 109 à 128 de la région de noyau de HCV : NH_2-$X_{11}X_{12}$DPR$X_{13}X_{14}$SRNX_{15}GX_{16}VIDTX_{17}TC-COOH (SEQ ID NO 54), et lesdits ecides aminés contigus contenant un épitope stimulant des lymphocytes T, et dans laquelle ledit polypeptide mime les propriétés de stimulation immunologique de lymphocytes T du polypeptide tel que représenté à la SEQ ID NO 9, et dans laquelle X_{11} représente P ou Q, X_{12} représente N ou T, X_{13} représente R ou H, X_{14} représente R ou K, X_{15} représente L ou V ou F, X_{18} représente K ou R, X_{17} représente L ou I.

14. Utilisetion suivant la revendication 13, pour la préparation d'une composition immunogéne de HCV ledit polypeptide comprenant ou contenent d'environ 8 à environ 20 acides aminés contigus sèlectionnès parmi la région comprise entre les positions d'acides aminés 109 à 128 de la région de noyau de HCV :

PTDPRRRSRNLGKVIDTLTC (SEQ ID NO 9 = peptide CORE 19).

15. Utilisation suivant la revendication 13, pour la préparation d'une composition immunogène de HCV, ledit polypeptide étant choisi parmi les peptides suivants :

NH_2-NX_{15}GX_{16}VIDTX_{17}-COOH (SEQ ID NO 96), et

NH_2-X_{15}GX_{16}VIDTX_{17}-COOH (SEQ ID NO 97).

16. Utilisation suivant la revendication 13, pour la préparation d'une composition immunogéne de HCV, ledit polypeptide étant choisi parmi les peptides suivants :

NLGKVIDTL (SEQ ID NO 98), et

LGKVIDTL (SEQ ID NO 117).

17. Utilisation d'un polypeptide d'environ 8 à environ 20 acides eminés pour la préparation d'une composition immunogène de HCV, ledit polypeptide comprenant ou contenant d'au moins 8 à environ 20 acides eminés contigus sélectionnès parmi la région comprise entre les positions d'acides aminés 73 é 92 de la région de noyau de HCV : NH_2-GX_1X_2WX_3X_4PGX_5PWPLYX_6NX_7GX_8G-COOH (SEQ ID NO 99), et lesdits ecides aminés contigus contenant un épitope de stimulant des lymphocytes T, et dans lequelle ledit polypeptide mime les propriétés de stimulation immunologique de lymphocytes T du polypeptide tel que représenté à la SEQ ID NO 6, et dans laquelle X_1 représente, R ou K, X_2 représente A, S ou T, X_3 représente A ou G, X_4 représente Q, K ou R, X_5 représente Y ou H, X_6 représente G ou A, X_7 représente E ou K, et X_8 représente C, M ou L.

18. Utilisation suivant la revendication 17, pour la prèparation d'une composition immunogéne de HCV, ledit polypeptide comprenant ou contenant d'au moins 8 à environ 20 acides aminés contigus sélectionnés parmi la région

comprise entre les positions d'acides aminés 73 à 92 de la région de noyau de HCV :

GRTWAQPGYPWPLYGNEGCG (SEQ ID NO 6 = peptide CORE 13).

19. Utilisation suivant la revendication 17, pour la préparation d'une composition immunogène de HCV, ledit polypeptide étant sélectionné parmi :

NH_2-$X_2WX_3X_4PGX_5PW$-COOH (SEQ ID NO 100), et

NH_2-$WX_3X_4PGX_5PW$-COOH (SEQ ID NO 101).

20. Utilisation suivant la revendication 17, pour la préparation d'une composition immunogène de HCV, ledit polypeptide étant sélectionné parmi :

TWAQPGYPW (SEQ ID NO 102), et

WAQPGYPW (SEQ ID NO 103).

21. Utilisation suivant l'une quelconque des revendications 1 à 20, dans laquelle ledit épitope de stimulant des lymphocytes T est un épitope de lymphocytes T auxiliaires.

22. Utilisation suivant l'une quelconque des revendications 1 à 20, dans laquelle ledit épitope de stimulant des lymphocytes T est un épitope CTL.

23. Utilisation suivant l'une quelconque des revendications 1 à 22, dans laquelle ledit polypeptide est incorporé dans une composition vaccinale prophylactique.

24. Utilisation suivant l'une quelconque des revendications 1 à 22, dans laquelle ledit. polypeptide est incorporé dans une composition vaccinale thérapeutique.

25. Polypeptide comprenant des répétitions multiples, des combineisons ou des mimotopes d'une quelconque des séquences d'acides aminés contigus sélectionnées pour qu'elles contiennent des épitopes stimulant des lymphocytes T comme défini suivant l'une quelconque des revendications 1 à 22, lesdites combinaisons comprenant deux peptides ou davantage joints en une structure unique et lesdits mimotopes présentant une ou plusieurs varietions d'acides aminés en comparaison desdits peptides pour autant que lesdits peptides mimotopes puissent procurer une stimulation immunologique, aprés quoi les lymphocytes T sont réactifs vis-à-vis d'au moins une souche de HCV.

26. Utilisation suivant l'une quelconque des revendications 1 à 24, ledit polypeptide étant un polypeptide recombinant exprimé à l'aide d'un vecteur d'expression comprenant un insert d'acide nucléique codant pour un polypeptide suivant l'une quelconque des revendications 1 à 22.

27. Utilisation suivant l'une quelconque des revendications 1 à 24, dans laquelle ledit polypeptide est lié de maniére fonctionnelle à un immunogéne apparenté à un pethogène, tel que les protéines d'enveloppe de HCV E1 et E2, ou les immogènes du HCV NS3, NS4 ou NSS, ou un peptide de HCV contenant un épitope de stimulant des lymphocytes B.

28. Peptide comprenant au moins 8 acides eminés contigus de la séquence d'un quelconque des peptides suivants, lesdits peptides contenant un épitope de lymphocytes T :

e)

NH_2-$X_{30}X_{31}X_{32}DGX_{33}NX_{34}X_{35}TGN$-$X_{36}$PGCSFSI-OOH (SEQ ID NO 51),

VLEDGVNYATGNLPGCSFSI (SEQ ID NO 13 = peptide CORE 27),

VLEDIVNYATGNLPGCSFSI (SEQ ID NO 73),

NH_2-$GX_{33}NX_{34}X_{35}TGN$-X_{36}-COOH (SEQ ID NO 74),

NH_2-$X_{33}NX_{34}X_{35}TGN$-X_{36}-COOH (SEQ ID NO 75),

NH_2-NX_{36}PGCSFSI-COOH (SEQ ID NO 76),

NH_2-X_{36}PGCSFSI-COOH (SEQ ID NO 77),

GVNYATGNL (SEQ ID NO 78),

NLPGCSFSI (SEQ ID NO 80), ou

LPGCSFSI (SEQ ID NO 81),

dans lequel ledit peptide mime les propriétés de stimulation immunologique de lymphocytes T du peptide représenté à la SEQ ID NO 13;

b)

NH_2-$GGX_{25}X_{26}X_{27}X_{28}LX_{29}HGVRX_{30}X_{31}X_{32}DGX_{33}NX_{34}$-COOH (SEQ ID NO 52),

GGAARALAHGVRVLEDGVNY (SEQ ID NO 12 = peptide CORE 25),

GGVAARALAHGVRVLEDGVNY (SEQ ID NO 118),

NH_2-$X_{28}LX_{29}HGVRX_{30}X_{31}$-COOH (SEQ ID NO 82),

NH_2-$LX_{29}HGVRX_{30}X_{31}$-COOH (SEQ ID NO 83),

NH_2-$GVRX_{30}X_{31}X_{32}DGX_{33}$-COOH (SEQ ID NO 84),

NH_2-$VRX_{30}X_{31}X_{32}DGX_{33}$-COOH (SEQ ID NO 85),

NH_2-$RX_{30}X_{31}X_{32}DGX_{33}NX_{34}$-COOH (SEQ ID NO 86),

NH_2-$X_{30}X_{31}X_{32}DGX_{33}NX_{34}$-COOH (SEQ ID NO 87),

ALAHGVRVL (SEQ ID NO 88),

LAHGVRVL (SEQ ID NO 89),

VRVLEDGV (SEQ ID NO 90),

RVLEDGV (SEQ ID NO 91),

VLEDGVNY (SEQ ID NO 92), ou

LEDGVNY (SEQ ID NO 93),

dans lequel ledit peptide mime les propriétés de stimulation immunologique de lymphocytes T du peptide représenté à la SEQ ID NO 12;
C)

NH_2-$LX_{19}X_{20}YIPX_{21}X_{22}GX_{23}PX_{24}GGX_{25}X_{26}X_{27}X_{28}LX_{29}$-COOH (SEQ ID NO 53),

LMGYIPLVGAPLGGAARALA (SEQ ID NO 11 = peptide CORE 23),

NH_2-$LX_{19}X_{20}YIPX_{21}X_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 62),

NH_2-$X_{19}X_{20}YIPX_{21}X_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 63),

NH_2-$YIPX_{21}X_{22}GX_{23}PX_{24}$-COOH (SEQ ID NO 64),

NH_2-$IPX_{21}X_{22}GX_{23}PX_{24}$-COOH (SEQ ID NO 65),

NH_2-$X_{21}X_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 66),

NH_2-$X_{22}GX_{23}PX_{24}GGX_{25}$-COOH (SEQ ID NO 68),

LMGYIPLV (SEQ ID NO 69),

MGYIPLV (SEQ ID NO 70),

YIPLVGAPL (SEQ ID NO 71),

IPLVGAPL (SEQ ID NO 72),

LVGAPLGGA (SEQ ID NO 94), ou

VGAPLGGA (SEQ ID NO 95),

dans lequel ledit peptide mime les propriétés de stimulation immunologique de lymphocytes T du peptide représenté à la SEQ ID NO 11;
d)

NH_2-$X_{11}X_{12}DPRX_{13}X_{14}SRNX_{15}GX_{16}VIDTX_{17}TC$-COOH (SEQ ID NO 54),

PTDPRRRSRNLGKVIDTLTC (SEQ ID NO 9 = peptide CORE 19),

NH_2-$NX_{15}GX_{16}VIDTX_{17}$-COOH (SEQ ID NO 96),

NH_2-$X_{15}GX_{16}VIDTX_{17}$-COOH (SEQ ID NO 97),

NLGKVIDTL (SEQ ID NO 98), ou

LGKVIDTL (SEQ ID NO 117),

dans lequel ledit peptide mime les propriétés de stimulation immunologique de lymphocytes T du peptide tel que représenté à la SEQ ID NO 9;
e)

NH_2-$GX_1X_2WX_3X_4PGX_5PWPLYX_6NX_7GX_8G$-COOH (SEQ ID NO 99),

GRTWAQPGYPWPLYGNEGCG (SEQ ID NO 6 = peptide CORE 13),

NH_2-$X_2WX_3X_4PGX_5PW$-COOH (SEQ ID NO 100),

NH_2-$WX_3X_4PGX_5PW$-COOH (SEQ ID NO 101),

TWAQPGYPW (SEQ ID NO 102), ou

WAQPGYPW (SEQ ID NO 103),

dans lequel ledit peptide mime les propriétés de stimulation immunologique de lymphocytes T du peptide tel que représenté à la SEQ ID NO 6;

dans lesquelles X_1 représente R ou K, X_2 représente A, S ou T, X_3 représente A ou G, X_4 représente Q, K ou R, X_5 représente Y ou H, X_6 représente G ou A, X_7 représente E ou K, X_8 représente C, M ou L, X_9 représente W ou L, X_{10} représente S, N, T, D ou H, X_{11} représente P ou Q, X_{12} représente N ou T, X_{13} représente R ou H, X_{14} représente R ou K, X_{15} représente L ou V ou F, X_{16} représente K ou R, X_{17} représente L ou I, X_{18} représente F ou L, X_{19} représente M ou I, X_{20} représente G ou E, X_{21} représente L ou V ou I, X_{22} représente V ou L, X_{23} représente A ou G, X_{24} représente L, V ou I, X_{25} représente A ou V, X_{26} représente A ou S, X_{27} représente R ou A, X_{28} représente A ou T ou E, X_{29} représente A ou E, X_{30} représente V ou A ou L, X_{31} représente L ou V ou I, X_{32} représente E ou G, X_{33} représente V ou I, X_{34} représente F ou Y, X_{35} représente A ou P et X_{36} représente L ou I.

29. Composition immunogéne contenant ou comprenant au moins un des peptides ou polypeptides suivent la revendication 28 mélangé avec un excipient pharmaceutiquement acceptable.

30. Composition vaccinale suivant la revendication 29.

31. Composition vaccinale prophylactique suivant la revendication 30.

32. Composition vaccinale thérapeutique suivant la revendication 30.

33. Composition suivant l'une quelconque des revendications 29 à 32, ladite composition comprenant en plus d'un quelconque des polypeptides suivent la revendication 28, un peptide ou un polypeptide contenant au moins un épitope stimulant des lymphocytes B de HCV, et/ou un polypeptide structurel de HCV, et/ou un polypeptide non structurel de HCV.

34. Composition suivant l'une quelconque des revendications 29 à 33, dans laquelle ledit polypeptide suivant la revendication 28 est mélangé à des particules de HBsAg ou de HBcAg, des immunogénes de HBV, des immunogénes de HIV et/ou des immunogènes de HTLV.

35. Utilisation d'un vecteur d'expression recombinant comprenant un insert d'acide nucléique codant pour un polypeptide tel que défini suivant l'une quelconque des revendications 1 à 22 pour la préparation d'une composition immunogéne de HCV.

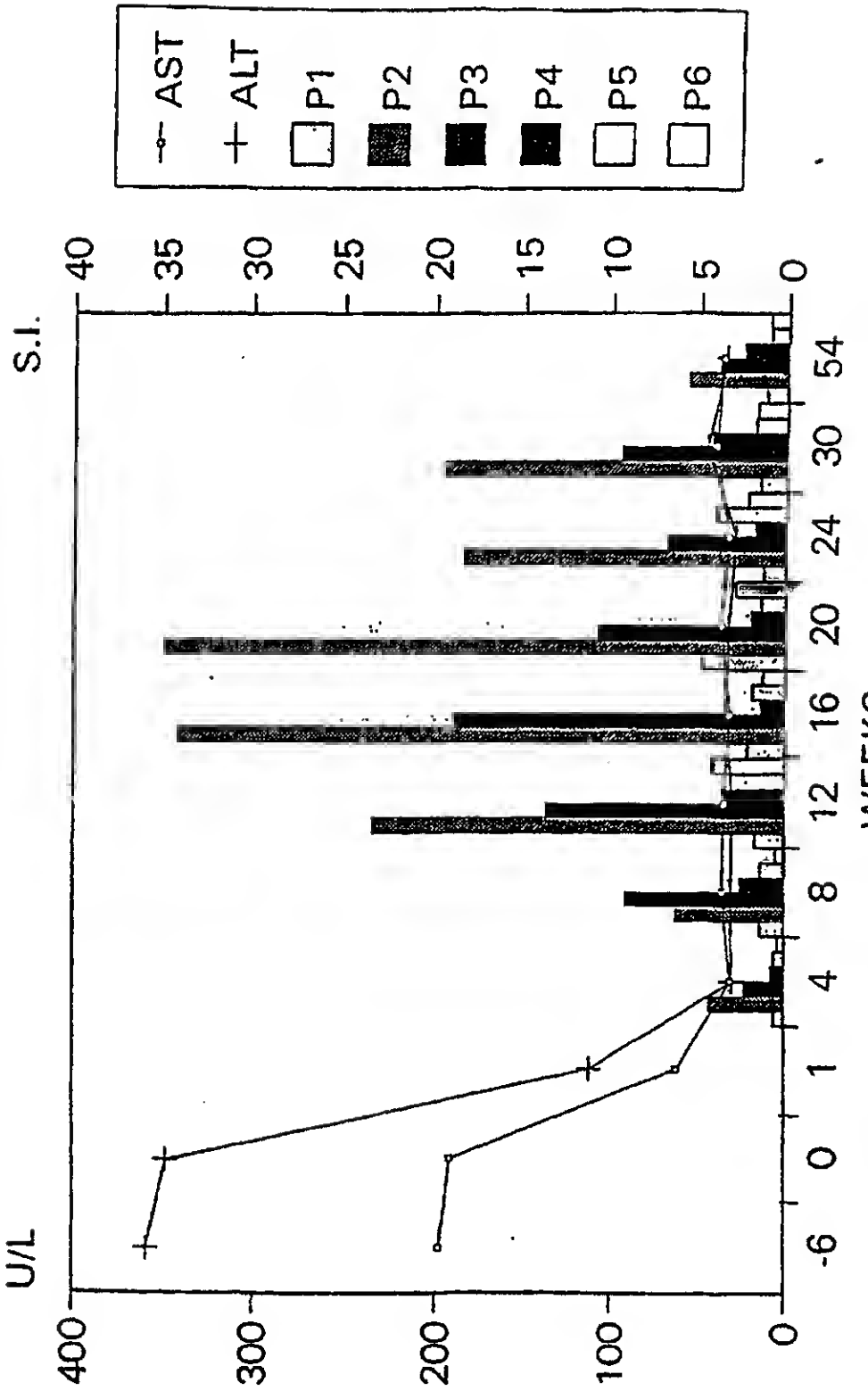

Figure 1. Evolution of lymphoproliferative responses and transaminase activities in HCV patient # 632

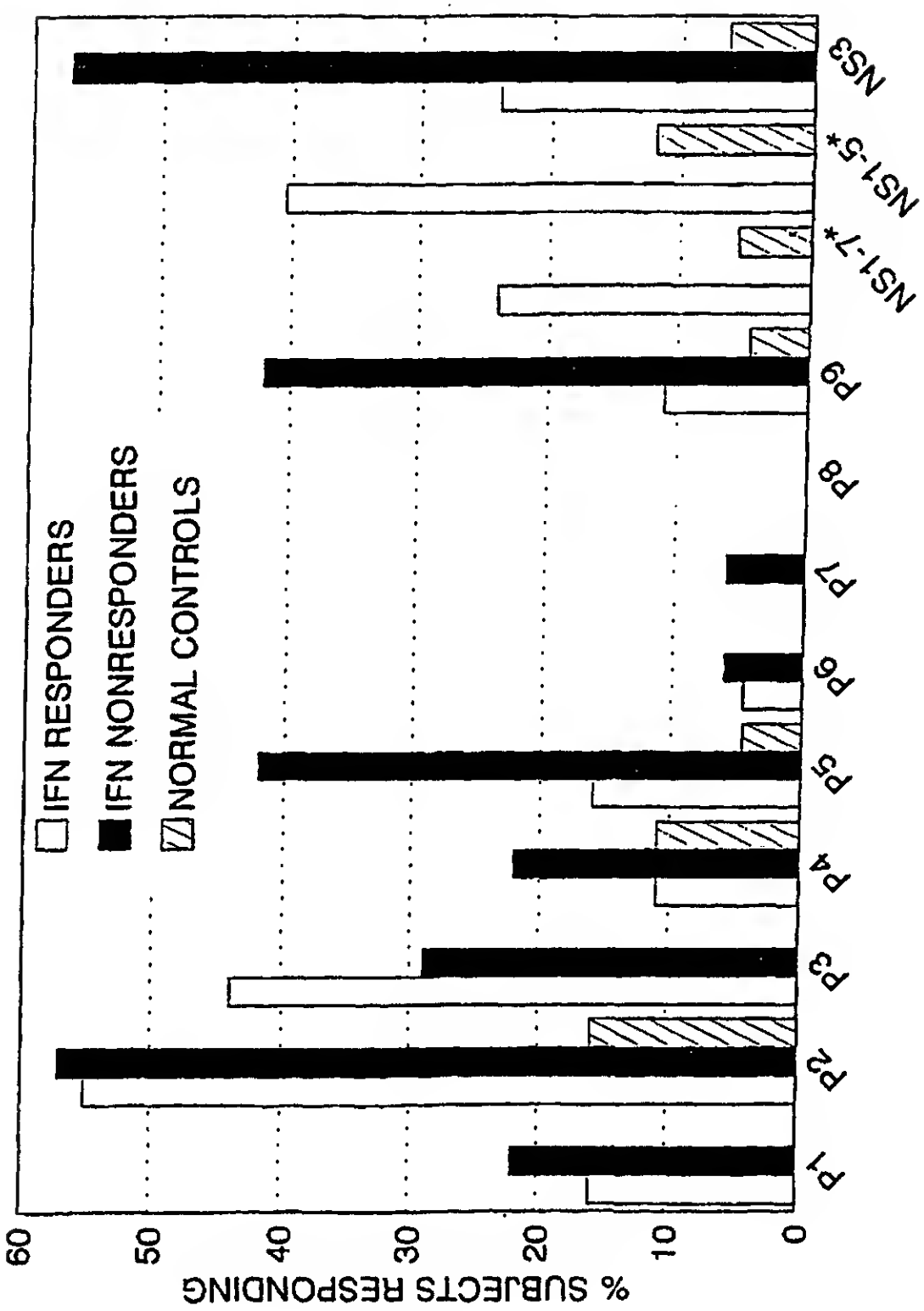
IFN RESPONDERS
IFN NONRESPONDERS
NORMAL CONTROLS
% SUBJECTS RESPONDING
0
10
20
30
40
50
60
P1
P2
P3
P4
P5
P6
P7
P8
P9
NS1-7*
NS1-5*
NS3

Figure 2

Figure 3

BE8309 NS3 SEQUENCE

GVAKAVDFVPVESMETTMRSPVFTDNSSPPAVPQTFQVAHLHAPTGSGKSTKVPAAYAA
QGYKVLVLNPSVAATLGFGAYMSKAHGVDPNIRTGVRTITTGAPITYSTYGKFLADGGC
SGGAYDIIICDECHSIDSTSILGIGTVLDQAETAGARLVVLATATPPGSVTVPHPNIEE
VALSSTGEIPFYGKAIPIEVIKGGRHLIFCHSKKKCDELAAKLSGFGINAVAYYRGLDV
SVIPTSGDVVVVATDALMTGFTGDFDSVIDCNTCVTQTVDFS

Figure 4

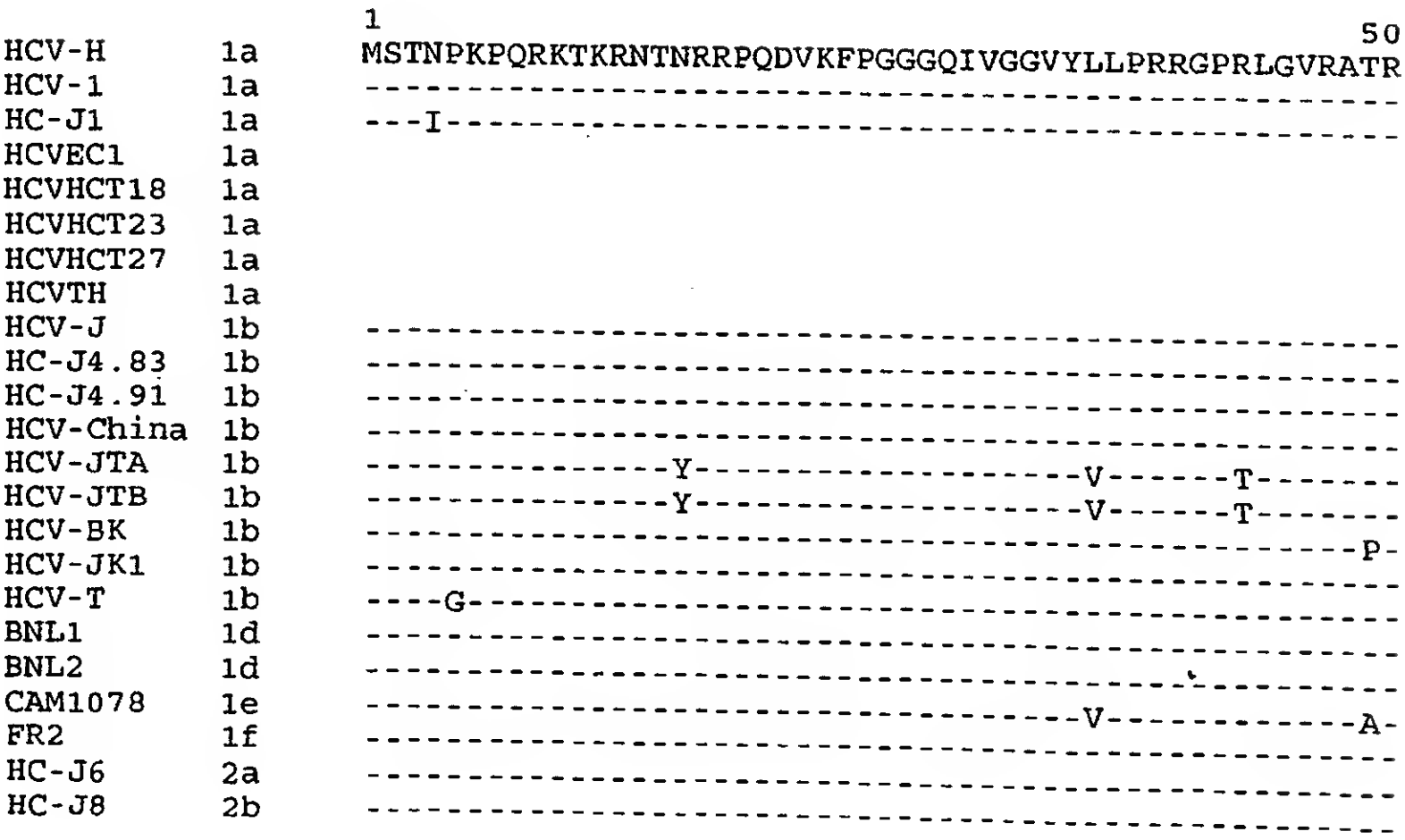

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Figure 4 - Continued 1

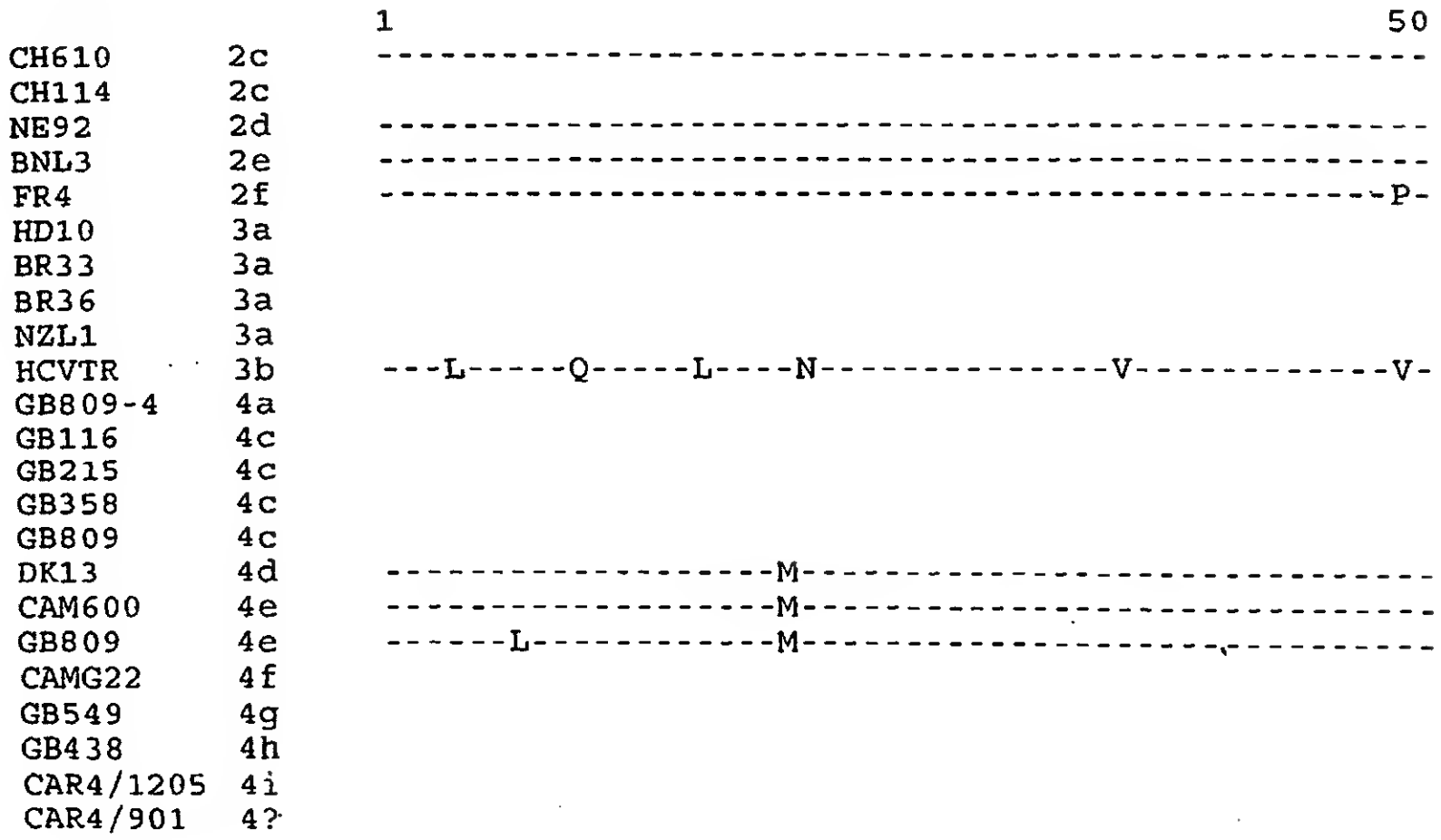

Figure 4 - Continued 2

```
                    1                                                  50
BNL7        4k      --------------------M-------------------------------
BE95        5a      ------------------------------------------M---------
BE100       5a
HK2         6a      ---L---------------T-------------------------------
FR1         7a      ---L---------------M-------------------------------
VN4         8a      ---L-----------I-----------------------------------
VN12        8b      ---L---------------M-------------------------------
VN13        9a      ---L-----------------------------------------------
NE98        10a     ---L------------X-------------------V------Q-----V-
```

Figure 4 - Continued 3

```
                        51                                                  100
HCV-H          1a       KTSERSQPRGRRQPIPKARRPEGRTWAQPGYPWPLYGNEGCGWAGWLLSP
HCV-1          1a       ----------------------------------------------------
HC-J1          1a       ----------------V-----------------------------------
HCVEC1         1a
HCVHCT18       1a
HCVHCT23       1a
HCVHCT27       1a
HCVTH          1a
HCV-J          1b       ----------------------------------------M---------
HC-J4.83       1b       ----------W-------------A---------------L---------
HC-J4.91       1b       ------------------Q----A---------------L---------
HCV-China      1b       ----------------------------------------F---------
HCV-JTA        1b       ----------------------A---------------L---------
HCV-JTB        1b       ----------------------A---------------L---------
HCV-BK         1b       ----------------------------------------L---------
HCV-JK1        1b       ------------------Q----A---------------L---------
HCV-T          1b       --W---------------Q----A---------------L------V--
BNL1           1d       --------------------X---S-----------------------
BNL2           1d       ---------D---------QSD--X-----H---------`---------
CAM1078        1e       ----------------E------
FR2            1f       ----------------------S-----------A-------------
HC-J6          2a       ----------------D--ST-KS-GK------------L---------
HC-J8          2b       ----------------D--ST-KS-GK----------------------
```

Figure 4 - Continued 4

```
                    51                                                  100
CH610       2c      ----------------D--TT-KS-GR----------L---------
CH114       2c
NE92        2d      ----------------D---T-KS-GK----------L---------
BNL3        2e      ----------------D-XAT--S-GR----------L---------
FR4         2f      ----------------D--AT-KS-GR----------L---------
HD10        3a
BR33        3a
BR36        3a
NZL1        3a
HCVTR       3b      ---------KQ-HL-----SR---S-----------K---L-------
GB809_4     4a
GB116       4c
GB215       4c
GB358       4c
GB809       4c
DK13        4d      --------------------QL---S-------------------------
CAM600      4e      --------------------T---S-------------------------
GB809       4e      --------------------S---S-------------------------
CAMG22      4f
GB549       4g
GB438       4h
CAR4/1205   4i
CAR4/901    4?
```

Figure 4 - Continued 5

```
                    51                                                  100
BNL7        4k      --------------------S---S--------------------X-----
BE95        5a      --------------------Q-T--S-G---------A---L---------
BE100       5a
HK2         6a      --------------------Q-Q--H-------------------------
FR1         7a      ------------------V-Q-T--S-G-----------------------
VN4         8a      ------------------V-HQT-----------------------------
VN12        8b      -------A---------V-QNQ-----------------------------
VN13        9a      ------------------V-HQT-----------------------------
NE98        10a     ---------S------R---T---S-------------------------
```

Figure 4 - Continued 6

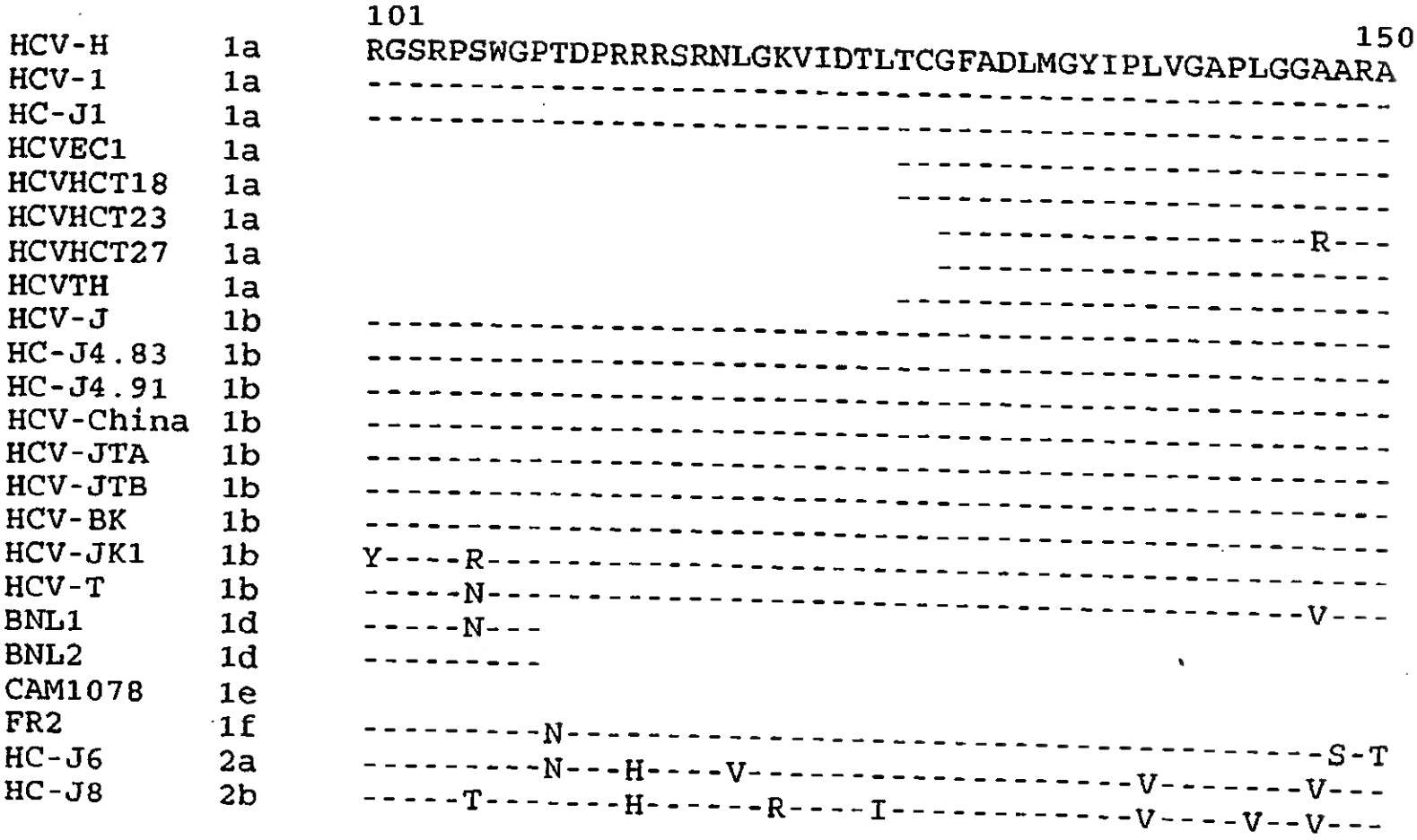

Figure 4 - Continued 7

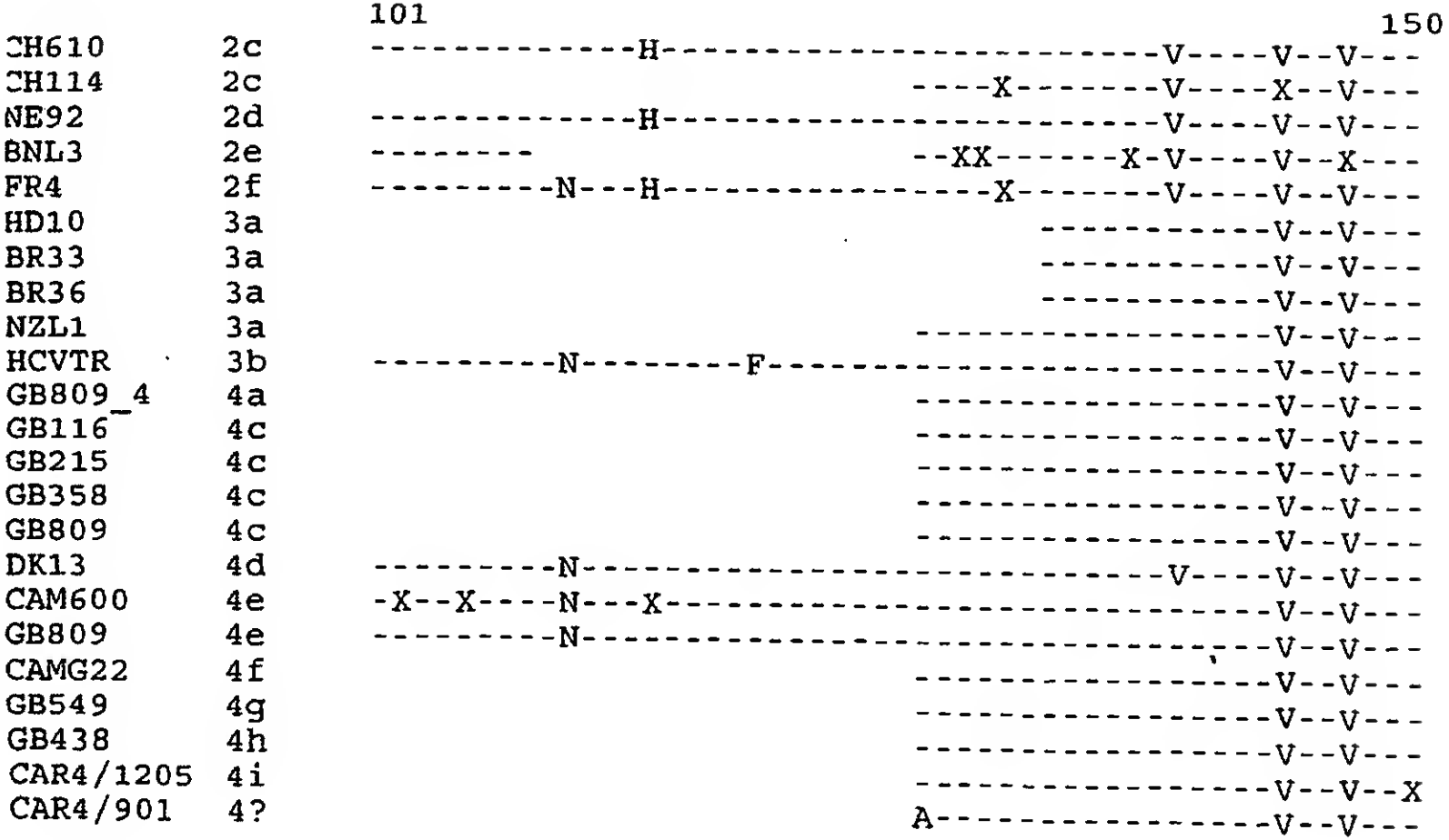

Figure 4 - Continued 8

```
                    101                                                 150
BNL7        4k      ---------N-------
BE95        5a      -----N---N----K-------------------------G-I--V---
BE100       5a                                    -------V-------G-V--V---
HK2         6a      -----H---N-----------------------------V-------V-A-
FR1         7a      -----N---N-----------------XXL---------VL-G----V-A-
VN4         8a      -----N---N-----------------------------V----X--V-X-
VN12        8b      -----D-X-N---X---------------------E---V-------V-AE
VN13        9a                X----N---N---X--------------XX----IE--
NE98        10a                                          ---------N-----
```

Figure 4 - Continued 9

```
                    151                                                 200
HCV-1        1a     LAHGVRVLEDGVNYATGNLPGCSFSIFLLALLSCLTVPASAYQVRNSTGL
HCV-H        1a     ----------------------------------------------S--
HC-J1        1a     ------------------------------------------------
HCVEC1       1a     ----------------------------------------------S--
HCVHCT18     1a     ------------------------------------------H-------
HCVHCT23     1a     ------------------------------------------------
HCVHCT27     1a     ----------------------------------------------S-I
HCVTH        1a     -------------------------L----------------------
HCV-J        1b     ------------------------------------I-----E---VS-I
HC-J4.83     1b     ------------------------------------I-----E---VS-I
HC-J4.91     1b     ------------------------------------I-----E---VS-I
HCV-China    1b     ------------------------------------T-----E---VS-I
HCV-JTA      1b     ------------------------------------I----------AS--
HCV-JTB      1b     ------------------------------------I----------RS--
HCV-BK       1b     ------------------------------------T-----E-H-VS-I
HCV-JK1      1b     ----------------------------------V-T-E---VS-V
HCV-T        1b     ------------------------------------I-----E-H-VS-I
BNL1         1d               ----------------------------XT-HE---AS-V
BNL2         1d               ----------------------F-------TT-HE---AS-V
FR2          1f     -X------XG--XXXXX--X---XX----X---------T---E-HST-DG
HC-J6        2a     -------------F--------------------I-T-V--AE-K-ISTG
HC-J8        2b     -----------I----------------------V---V--VE---ISSS
CH610        2c     -----------I----------------S-----IS--V--VE-K-TSTS
```

Figure 4 - Continued 10

```
                       151                                              200
S83       2c                                                     VE-KDTGDS
CH114     2c           -----------IX-----M--------------XIS--V--XE---TST-
NE92      2d           -----------I----------------------I---V-GL--K-TSSS
BNL3      2e           --X--------I--X------------X------V---V-XVE-K-TSQA
FR4       2f           -----------I----------------------I---V--I--K-NSHF
BNL4      2g                    -------------------------V---V--V--K-TSTM
BNL5      2h                    --I-----------------------------V--K-TSHS
BNL6      2i                    --I----------------------I---V--V--A-RS-S
HD10      3a           ------A----I-F-----------------F---IH--ASLEW--TS--
BR33      3a           ------A----I-F-----------------F---IH--AGLEW--TS--
BR36      3a           ------A----I-F-----------------F---IH--ASLEW--TS--
NZL1      3a           ------A----I-F-----------------F---IH--ASLEW--TS--
HCV-TR    3b           ------A-G----------------------F----C---GLEYT-TS--
GB809_4   4a           ------AV---I-----------------------------EHY--AS-I
Z4        4a                                                    EHY--AS-I
Z1        4b                                                    VHY--AS-V
GB116     4c           -E----AV---I--------------S-----------T--VNY--AS-V
GB215     4c           -E----AV---I--------------Y-----------T--IHY--AS-V
GB358     4c           ------AV---I--------------------------T--VNY--AS-I
Z6        4c                                                    VNY--AS-V
Z7        4c                                                    VNYH-AS-V
DK13      4d           ------L----------------------------------NY---S-V
CAM600    4e           ------AV---I--------------------------T--VNY--AS-I
```

Figure 4 - Continued 11

```
                   151                                              200
GB809       4e     ------AV---I----------------------------GVNY--AS-V
CAMG22      4f     ------AV---I-----------------------------VHYH-TS-I
CAMG27      4f     ------AV---I-----------------------------VHYH-TS-I
GB549       4g     ------AV---I-----------------------------QHY--IS-I
GB438       4h     ------AV---I-----------------V---R-------QHY--AS-I
CAR4/12054  4i     ------A----I--------------S--E-----------IHY--ASDG
CAR4/901    4?     ------AV---I--------------X--------------QHY--VS-I
BNL7        4k              --I-F---------------------------INY--VS-I
BNL8        4k              --I-----------------------------INY--TS-I
BNL9        4k              --I-----------------------------INYH-TS-I
BNL10       4k              --I------I---X-----X------------TNY--VS-I
BNL11       4k              --I-----X-----------------------TNY--VS-I
BNL12       4l              --I---------------I-------------QHY--VS-I
GB724       4?
BE95        5a     ---------------------------I-------------VPY--AS-I
BE100       5a     ---------------------------I-------------VPY--AS-I
SA4         5a                                              VPY--AS-V
HK2         6a     ------AI---I------------------------T----LTYG--S--
FR1         7a     ------AI----------------------------T----I--K-AS-I
VN4         8a     -----XXI--X-----X---XX-X--X---------T----AHYT-KS--
VN12        8b     -X----AI---I---------------X--------T----LNYA-KS--
NE98        10a             --I-F-----------------F---LT-TAGLEY--AS--
```

Figure 4 - Continued 12

```
                        201                                              250
HCV-1        1a         YHVTNDCPNSSIVYEAADAILHTPGCVPCVREGNASRCWVAMTPTVATRD
HCV-H        1a         -----------V-----------------------------V--------
HC-J1        1a         ----------------H-----------------V---------------
HCVEC1       1a         -----------------------------H---V----------------
HCVHCT18     1a         -----------------------------H---V------V---------
HCVHCT23     1a         ----------------------A--------D-V------V------K--
HCVHCT27     1a         ---------------T--T---S------------K---PVA--------
HCVTH        1a         ----------------------A---------------------------
HCV-J        1b         -------S----------M-M-----------S-F------L---L-A-N
HC-J4.83     1b         -------S----------M-M-----------D-S------L---L-A-N
HC-J4.91     1b         -------S----------V-M-------------S------L---L-A--
HCV-China    1b         -------S----------L-M-------------S------L---L-A-N
HCV-JTA      1b         -------S---------GM-M-----------N--------L---L-A-N
HCV-JTB      1b         -------S---------GM-M-----------N-V------L---L-A-N
HCV-BK       1b         -------S-A--------L-M-------------S------L---L-A-N
HCV-JK1      1b         -------S----------M-M-------------S------L---L-A-N
HCV-T        1b         -------S----------M-M-----------N-S------L---L-A-N
BNL1         1d         -------S----I--MDGM-M-Y---------D-HL---M-L---L-VKX
BNL2         1d         --L----S----I--MSGM---A---------N-S----MXL---L-VK-
FR2          1f         -------S-G------K-I------X---I----I-----PL---L-A-I
HC-J6        2a         -M-----T-D--TWQLQA-V--V------EKV--T----IPVS-N--VQQ
HC-J8        2b         -YA----S-N--TWQLT--V--L------ENDNGTLH--IQV--N--VKH
CH610        2c         -M-----S-----WQLEG-V---------EQI--------PVS-N--I-Q
```

Figure 4 - Continued 13

```
                    201                                               250
S83       2c        -MP----S-----WQLEG-V---------E-TA-V-----PVA-NL-ISQ
CH114     2c        -M-----S-----WQLEG-VX-I------EWTNTTP----PVS-X--I-Q
NE92      2d        -M-----Q-----WQLR--V--V------EEK--I----IPVS-NI-VSQ
BNL3      2e        -MA----S-N---WQLX--V--V------ENSSGRFH--IPIS-NI-VSK
FR4       2f        -MA----A-D---WQLR--V--V------E-S--RTF--T-VS-N--VSR
BNL4      2g        -MA----S-N--IWQMQG-V--V------ELQ--K----IPV--N--VNQ
BNL5      2h        -M-----S-----WQLK--V--V------E-HQ-Q----IPV--N--VSQ
BNL6      2i        -M-----S-----WQLEE-V--V------EWKD-T----IPV--NI-VSQ
HD10      3a        -VL----S--------D-V-----------QD--T-A--TPV-----V-Y
BR33      3a        -VL----S--------D-V---A-------QD--T-T--TPV-----V-Y
BR36      3a        -VL----S--------D-V------I----QD--T-T--TPV-----VKY
NZL1      3a        -VL----S--------D-V-----------QD--T-T--TPV-----V-Y
HCV-TR    3b        -VL----S-G------E-V---L-------TT--Q-S--TTVST---V-T
GB809-4   4a        --I--------V---TDHH---L--------A--V----TPV-----AVS
Z4        4a        --I-------------DHH---L-------MT--T----TPV-----VAH
Z1        4b        ---------T-----TEHH-M-L--------TE-T-----PL-----APY
GB116     4c        --I-------------DYH---L--L-----V--Q------L-----APY
GB215     4c        ----------------DHH---L--L-----V--Q------LS----APY
GB358     4c        --I------------TEHH---L--L-----V--Q------L-----APY
Z6        4c        ----------------EHQ---L--L-----V--Q------L-----VSY
Z7        4c        --I--------M---EHH---L-----------Q------L-----APY
DK13      4d        ---------------TDYH---L-----------K-T---SL-----AQH
CAM600    4e        --I------A-----TENH---L--------T--Q------L-----SPY
```

Figure 4 - Continued 14

```
                  201                                                  250
GB809      4e     --I------A-----TDNH---L-------KT--Q------L-----SPY
CAMG22     4f     --L----------F--VHH---L--------T--Q------L---L-APY
CAMG27     4f     --I----------F--EHH---L--------T--Q----I-L---L-APH
GB549      4g     ----------------DHH-M-L--------T--T-----PL-----APY
GB438      4h     ----------------DHH-M-L--------T--V----IPL-----VPY
CAR4/12054 4i     -YI-------------ENH---L--I----KT--Q------L---L-APH
CAR4/901   4?     ----------------DHH-M-L--I-----T--V-----SL-----APY
BNL7       4k     -Y--------------DHH---L----------Q------L-----APY
BNL8       4k     ----------------DHH---L--------T--Q------L-----APY
BNL9       4k     --I-------------DHH---L--------V--Q-S----L---I-APY
BNL10      4k     ----------------DHH--AL--------V--Q------L-----APY
BNL11      4k     -------------F--DHH---L-------K---H------L-----APY
BNL12      4l     ---------------SDHH---L-------KT--T------L-----API
GB724      4?     --I--------V---TDHH---L--------T--V----TPV-----AVS
BE95       5a     ----------------DNL---A-------MT--V-----QI---LSAPS
BE100      5a     ----------------D-L---A--------KD-V-----QI---LSAPS
SA4        5a     ----------------DNL---A--------QD-V-K---QI---LSAPN
HK2        6a     --L----------L--DAM---L---L----VDDR-T--H-V---L-IPN
FR1        7a     --L----S-N---F--ETM---L------IKA--E----LPVS--L-VPN
VN4        8a     --L------------ETL---L-------KXX-Q-----QAS--L-VPN
VN12       8b     --L------------NGM---L-------KT--LTK--LSAS--L-VQN
NE98       10a    -M-----S-G------G-I---L--------S--T----IPVSX---VKS
```

Figure 4 - Continued 15

```
                  251                                                  300
HCV-1       1a    GKLPATQLRRHIDLLVGSATLCSALYVGDLCGSVFLVGQLFTFSPRRHWT
HCV-H       1a    ----T-------------------------------------------H---
HC-J1       1a    ----------------------------------------I-----------
HCVEC1      1a    ---T--------------------------------------------------
HCVHCT18    1a    ---T--------------------------------------------------
HCVHCT23    1a    ---T-----------------------------I----------------
HCVHCT27    1a    N--------------------------------------------------
HCVTH       1a    R--T-----------------------------I----------------
HCV-J       1b    SSI-T-TI---V-----A-A----M----------S---------YE-
HC-J4.83    1b    ASV-T-TI---V-----A-AF---M----------S----------E-
HC-J4.91    1b    ASV-T-TI---V-----T-AF---M--------I---S----------E-
HCV-China   1b    ATI-TATV---V-----A-AFS--M----------S---------YE-
HCV-JTA     1b    TSI-T-TI---V-----A-AF---M----------S---------YE-
HCV-JTB     1b    TSI-T-TI---V-----A-AF---M----------S---------YE-
HCV-BK      1b    VTI-T-TI---V-----A-AF---M----------S----------V-
HCV-JK1     1b    SSI-T-TI---V-----A-A----M----------S---------YE-
HCV-T       1b    NSV-TATI---V-----A-AF---M----------S--------- YE-
BNL1        1d    ASV-TXAI---V-----XX-F---M--X--------A---------M-H-
BNL2        1d    ANV-TAAI---V-----T-AFR--M-------------------'--LYH-
FR2         1f    ANA-IDEV---V-----A-VF---M-I-----G----------TS-----
HC-J6       2a    PGALTQG--T---MV-M---------------G-M-AA-M-IV--QH--F
HC-J8       2b    RGALTRS--T-V-MI-MA--A--------V--A-MILS-A-MV--Q--NF
CH610       2c    PGTLTKG--A-V-VI-M----------V--ALMIAA-AVIA--Q--TF
```

Figure 4 - Continued 16

```
                 251                                                                  300
S83        2c    PGALTKG--A---II-M---V--------V--ALM-AA-VVVV--QH-TF
CH114      2c    PGALTKG--A---VI-M-----------V--ALMIAA-AVVA--Q--XF
NE92       2d    PGALTKG--T---TIIA---F-----I-----A-M
BNL3       2e    PGALTKG--AR--AV-M-----------V--A-MIAA-A-IVA-K--YF
FR4        2f    PGALTRG--A---TI-M---------I-----A-MIAA-VAVV--QY-TF
BNL4       2g    PGALTRG--T---TI-MV--------I--V--A-MIAA-VVIV--QH-NF
BNL5       2h    PGALTRG--T---TI-A---V--------F--A-M--S-F-MI--QH-IF
BNL6       2i    PGAXTKG--T---II-A---F------
HD10       3a    VGATTASI---V-M---A--M--------M--A------A---R----Q-
BR33       3a    VGATTASI-S-V-----A--M--------M--A------A---R----Q-
BR36       3a    VGATTASI-S-V-----A--M--------M--A------A---R----Q-
NZL1       3a    VGATTASI-S-V-----A--M--------M--A------A---R----Q-
HCV-TR     3b    LGVTTASI-T-V-M---ARQ---------AF-A------A---R----T-
GB809_4    4a    MDA-LESF---V--M--A--V--V--------GA-----M---Q------
Z4         4a    PGA-LESF---V--M--A-------------GA--M--MI--R------
Z1         4b    PNA-LESM---V--M--A--M---F-I-----G--------D-R------
GB116      4c    VGA-LES--S-V--M--A--V-----I-----G------M-S-Q------
GB215      4c    IGA-VESF---V-MM--A--V-----I-----G------M-S-R------
GB358      4c    IGA-LES--S-V--M--A--A-----I-----G------M-S-Q------
Z6         4c    IGA-LDS----V--M--A--V-----------GA-----M-S-Q------
Z7         4c    IGA-LESI---V--M--A--V-----I-----G------M-S-Q------
DK13       4d    LNA-LES----V--M--G--------I--V--G----------Q------
CAM600     4e    AGA-LEP----V--M--A--M-----I-----GL-----M---Q------
```

Figure 4 - Continued 17

```
                          251                                              300
GB809        4e    VGA-LEP----V--M--A--V-----------GL-----M---Q------
CAMG22       4f    LGA-LESM---V--M--T--------------GI--A--M---R--L---
CAMG27       4f    IGA-LESM---V--M--T--------I-----GI-----M-N-R--L---
GB549        4g    VGA-LESM---V--M--A--V-----I-----G------M---R--L---
GB438        4h    LGA-L-SV-Q-V--M--A--------I--H--G---A--MVS-Q------
CAR4/12054i        LRA-LSS--A-V--M--A--A---F-I-----G---A-----IR--I-E-
CAR4/901     4?    LGA-L-S----V--M--A--------------G------M---Q------
BNL7         4k    IGA-LES--S-V--M--A--V-----I--X-XGL-----M-S-R------
BNL8         4k    IGA-LES--S-V--M--A--V-----I-----GL-----M-S-R------
BNL9         4k    IGA-LES--S-V--M--A--V-----I-----GA-----M-S-R------
BNL10        4k    TAA-LES--S-V--M--A--V-----I-X---GL-----M-SXQ------
BNL11        4k    IGA-LES--S-V-VM--A--V-----I-----GL-----M-S-R------
BNL12        4l    LSA-LMSV---V--M--A---S----------GA-----M---Q------
GB724        4?    VDA-LESF---V--M--A-----V--------GA-----M---Q------
BE95         5a    LGAVTAP---AV-Y-A-G-A---------A--AL-----M--YR--Q-A-
BE100        5a    FGAVTAP---AV-Y---G-A---------A--AL-----M--YR--Q-A-
SA4          5a    LGAVTAP---AV-Y-A-G-A---------A--A------M--YR--Q-T-
HK2          6a    AST---GF---V---A-A-VV--S--I------L--A------Q------
FR1          7a    SSV-IHGF---V-----A-AF---M-I------II--------R-KY-QV
VN4          8a    AST-V-GF-K-V-IM--A-AF---M-------GL--------LR--M-QV
VN12         8b    ASVSIRGV-E-V-----A-AF---M-------GL---------R--MYEI
NE98         10a   PCAATAS--T-V-MM-XA--------------AL--X--G-SWRH-Q---
```

Figure 4 - Continued 18

```
                301                                                  350
HCV-1      1a   TQGCNCSIYPGHITGHRMAWDMMMNWSPTTALVMAQLLRIPQAILDMIAG
HCV-H      1a   --D----------------N--------A---V----------M-----
HC-J1      1a   ----------------------------A--------------------
HCVEC1     1a   -------
HCVHCT18   1a   ------------------
HCVHCT23   1a   --D---------------
HCVHCT27   1a   --D---------------
HCVTH      1a   ------------------
HCV-J      1b   V-D----------VS--------------------VS---------VV--V--
HC-J4.83   1b   V-D----------LS--------------------VS---------VV--V--
HC-J4.91   1b   V-D----------VS--------------------VS---------VV--V--
HCV-China  1b   I-D----------V---------------------VS---------VM--VV-
HCV-JTA    1b   V-D----------VS--------------------VS---------VV--V--
HCV-JTB    1b   V-D----------VS--------------------VS---------VV--V--
HCV-BK     1b   L-D----------VS--------------------VS---------VV--V--
HCV-JK1    1b   V-D----L----VS--------------------VS---------VV--VV-
HCV-T      1b   V-D----------V---------------------VS---------VV--VG-
BNL1       1d   --E------
BNL2       1d   --E------
FR2        1f   V-D-------S-------XXX
HC-J6      2a   V-D---------T-----------------ATMIL-YAM-V-EV-I-I-G-
HC-J8      2b   --E-------Q-------------LS----LTMIL-YAA-V-ELV-EI-F-
CH610      2c   V-E---------------X
```

Figure 4 - Continued 19

		301 319
S83	2c	V-E--------R-------
CH114	2c	V-E---------------X
NE92	2d	V-D----------------
BNL3	2e	V-E----------------
FR4	2f	V-E---------------X
BNL4	2g	S-D-----
BNL5	2h	V-D-----
BNL6	2i	
HD10	3a	V-T----L----LS-----
BR33	3a	V-T----L----LS-----
BR36	3a	V-T----L----LS-----
NZL1	3a	V-T----L----LS-----
HCV-TR	3b	V-T---------VS-----
3B809_4	4a	--D------T---------
Z4	4a	--E------T---------
Z1	4b	--D---------VS-----
3B116	4c	--D------A--V------
3B215	4c	--D------A------G--
3B358	4c	--D------A--V------
Z6	4c	--D------A---------
Z7	4c	--D------A--V------
DK13	4d	--D------T---------
CAM600	4e	--D------T---------

Figure 4 - Continued 20

		301 319
GB809	4e	--D------A---------
G22	4f	--E----T----------
G27	4f	--E----------------
GB549	4g	--D------D---------
GB438	4h	--D------V---------
CAR4/12054	4i	--D------S-----XXXX
BNL7	4k	--D-----
BNL8	4k	A-D-----
BNL9	4k	--D-----
BNL10	4k	--D-----
BNL11	4k	--E-----
BNL12	4l	V-D-----
CAR4/901	4?	--D------V---------
GB724	4?	--D------T---------
BE95	5a	V-N------S--V------
BE100	5a	V-D------S--V---Q--
SA4	5a	V-D------S---------
HK2	6a	V-D------T--V------
FR1	7a	--D----XNX--V------
VN4	8a	V-E------T---------
VN12	8b	A-D------A---------
NE98	10a	V-D-----

<u>Figure 4</u> - Continued 21

```
                       351                                  400
HCV-1       1a   AHWGVLAGIAYFSMVGNWAKVLVVLLLFAGVDA|ETHVTGGSAGHTVSGF
HCV-H       1a   ---------K-----------------------|-------N--R-TA-L
HC-J1       1a   ---------------------------------|--I-S--Q-ARAM--L
HCVEC1      1a
HCVHCT18    1a
HCVHCT23    1a
HCVHCT27    1a
HCVTH       1a
HCV-J       1b   --------L--Y----------I-M-------G|H------RVASSTQSL
HC-J4.83    1b   --------L--Y----------I-A-------G|--YTS--A-S--T-TL
HC-J4.91    1b   --------L--Y----------I-A-------G|A-YTS--V--R-T---
HCV-China1b      --------L--YA---------I-M-------G|D-YAS--AQ-RSTL--
HCV-JTA     1b   --------L--Y----------I-M-------G|V-YT----QARHTQSV
HCV-JTB     1b   --------L--Y----------I-M-------G|V-YT----QARHTQ-V
HCV-BK      1b   --------L--Y--A-------I-M-------G|D------AQAK-TNRL
HCV-JK1     1b   --------L--Y----------I-M-------G|T-Y-SV-H-SQ-TRRV
HCV-T       1b   --------L--Y----------I-M-------G|S-I-S--TVAR-THSL
BNL1        1d
BNL2        1d
FR2         1f
HC-J6       2a   -----MF-L-----Q-A----V-I---A-----|Q--TV---TA-NARTL
HC-J8       2b   G----VF-L-----Q-A----IAI---V----- T-YSS-QE--R--A--
```

Figure 4 - Continued 22

```
                       401                                          450
HCV-1       1a         VSLLAPGAKQNVQLINTNGSWHLNSTALNCNDSLNTGWLAGLFYHHKFNSS
HCV-H       1a         -G--T------I----------I--------E-----------Q------
HC-J1       1a         ---FT------I----------I--------E----------I-Q------
HCVEC1      1a
HCVHCT18    1a
HCVHCT23    1a
HCVHCT27    1a
HCVTH       1a
HCV-J       1b         --W-SQ-PS-KI--V-------I-R---------Q--FI-A---A-R--A-
HC-J4.83    1b         A--FS---S-RI--V-------I-R---------H--F--A---T-R----
HC-J4.91    1b         T--FSS--S-KI--V-------I-R---------H--F--A---T------
HCV-China   1b         T--FT---S-KI----------I-R------------F--A---T-R--A-
HCV-JTA     1b         T-FFTQ-PA-RI----------I-R------E-----FF-A---A------
HCV-JTB     1b         A-FFT--PA-KI----------I-R------E-----FF-A---A------
HCV-BK      1b         --MF-S-PS-KI----------I-R---------Q--F--A---T-S----
HCV-JK1     1b         A-FFS--SA-KI--V-------I-R------E-I---FF-A---VK-----
HCV-T       1b         A--FTQ--S-KI----------I-R---------Q--F--S---A-R--A-
BNL1        1d
BNL2        1d
FR2         1f
HC-J6       2a         TGMFSL--R-KI----------I-R---------H--F--S---T-S----
HC-J8       2b         AG-FTT-----LY---------I-R---------Q--F--S---T------
```

Figure 5

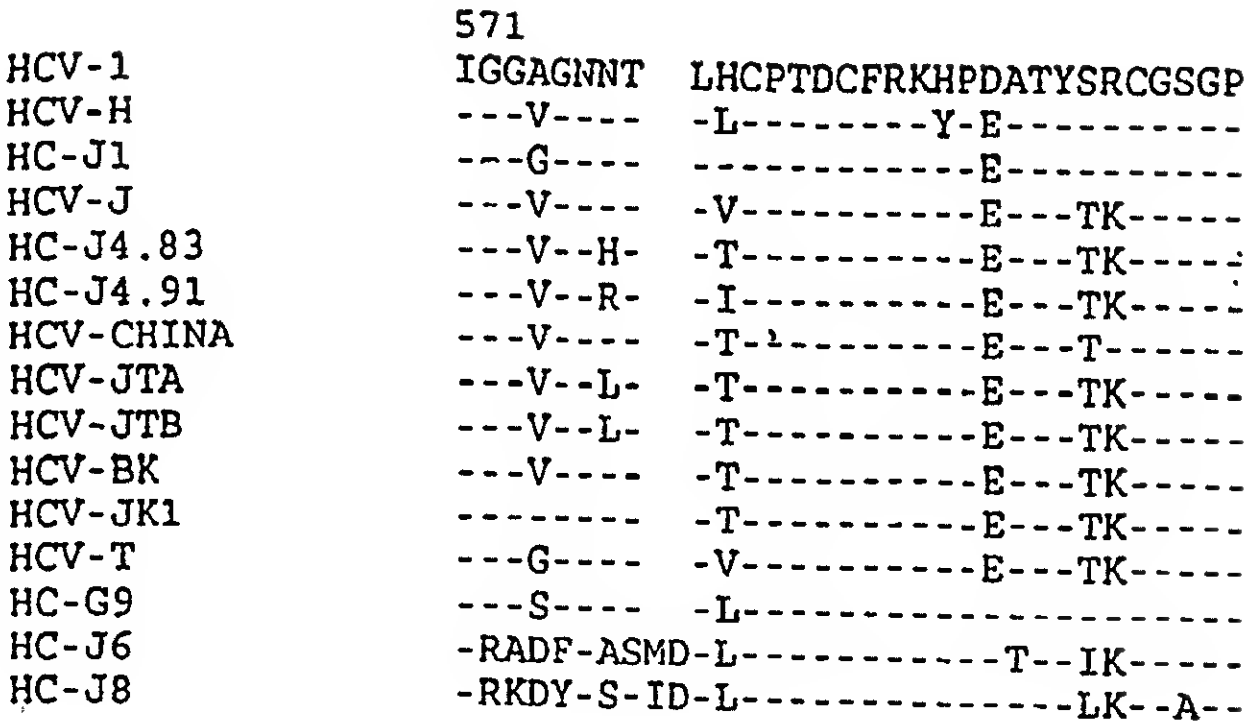
571
HCV-1 IGGAGNNT LHCPTDCFRKHPDATYSRCGSGP
HCV-H ---V---- -L--------Y-E----------
HC-J1 ---G---- ----------E----------
HCV-J ---V---- -V----------E---TK-----
HC-J4.83 ---V--H- -T----------E---TK-----
HC-J4.91 ---V--R- -I----------E---TK-----
HCV-CHINA ---V---- -T---------E---T------
HCV-JTA ---V--L- -T----------E---TK-----
HCV-JTB ---V--L- -T----------E---TK-----
HCV-BK ---V---- -T----------E---TK-----
HCV-JK1 -------- -T----------E---TK-----
HCV-T ---G---- -V----------E---TK-----
HC-G9 ---S---- -L----------
HC-J6 -RADF-ASMD-L----------T--IK-----
HC-J8 -RKDY-S-ID-L----------LK--A--

Figure 5 continued 1

	604
HCV-1	WITPRCLVDYPYRLWHYPCTINYTIFKIRMYVGGVEH
HCV-H	R-----M----------V---------
HC-J1	----------V---------
HCV-J	-L----M----------V-F-V--V---------
HC-J4.83	-L----------F-FS---V---------
HC-J4.91	-L----------L-FS---V---------
HCV-CHINA	-L----------V-FA---V---------
HCV-JTA	-L----I----------V-F----V---------
HCV-JTB	-L----I----------V-F----V---------
HCV-BK	-L----M----------V-F----V---------
HCV-JK1	-L----M----------F-F----------
HCV-T	-L----M----------V-F----V---------
HC-G9	-L----------V---------F------
HC-J6	-L-----I----------V----------
HC-J8	-L----------V-F----A---------

EP 0 725 824 B1

```
                1188        1200
HCV-1           GVAKAVDFIPVEN
HCV-H           -------------
HC-J1           ------------S
HC3-J           ------------S
BE8309          --------V---S
HC-J4.83        ------------S
HC-J4.91        ------------S
HCV-CHINA       ------------T
HCV-JTA         ------------S
HCV-JTB         ------------S
HCV-BK          --------V---S
HCV-JK1         ------------S
HCV-T           --------V---S
HC-J6           ----SI------T
HC-J8           ----SI------S

                1201                                                1250
HCV-1           LETTMRSPVFTDNSSPPVVPQSFQVAHLHAPTGSGKSTKVPAAYAAQGYK
HCV-H           ----------------A--------------------------K---
HC-J1           ----------------A-----------------------------
HCV-J           M---------------A---T-------------------------
BE8309          M---------------A---T-------------------------
HC-J4.83        M---------------A---T-------------------------
HC-J4.91        M---------------A---T-------------------------
HCV-CHINA       M---------------A---T-------------------------
HCV-JTA         M---------------A---T-------------------------
HCV-JTB         M---------------A---T----------------------X---
HCV-BK          M---------------A-----------------------------
HCV-JK1         M---------------A---T-------------------------
HCV-T           M---------------A---A-------------------------
HC-J6           -DIVT---T-S---T--A---TY--GY-------------V--------
HC-J8           -DVAT-T-S-S---T--A----Y--GY-----------------S----

                1251                                                1300
HCV-1           VLVLNPSVAATLGFGAYMSKAHGIDPNIRTGVRTITTGSPITYSTYGKFL
HCV-H           ----------------------V-----------------------
HC-J1           ------------------------------------------------
HCV-J           ----------------------E-------------G-------C---
BE8309          ----------------------V-------------A-----------
HC-J4.83        ------------------P-----------------G-----------
HC-J4.91        ------------------------------------GS----------
HCV-CHINA       ----------------------V-------------A-----------
HCV-JTA         ----------------------T-------------A-----------
HCV-JTB         ----------------------T-------------G-----------
HCV-BK          ------------------------------------A-V---------
HCV-JK1         ----------------------V----S---------A-----------
HCV-T           ----------------------V-------------A-----------
HC-J6           ----------------L------N---------V---A-----------
HC-J8           ----------------------N---------V---DS---------I
```

Figure 6

```
                1301                                                1350
HCV-1           ADGGCSGGAYDIIICDECHSTDATSILGIGTVLDQAETAGARLVVLATAT
HCV-H           --A--------------------S----------------------------
HC-J1           -------------------------V--------------------------
HCV-J           ----------------------S-T--------------------------
BE8309          --------------------I-S----------------------------
HC-J4.83        ----------------------S-T--------------------------
HC-J4.91        ----------------------S-T--------------------------
HCV-CHIHA       ----------------------S-T--------------------------
HCV-JTA         ----------------------S-T--------------------------
HCV-JTB         ----------------------S-T--------------------------
HCV-BK          ----------------------S-T--------------------------
HCV-JK1         ----------------------S----------------------A--
HCV-T           ------------M--------S-T--------------------------
HC-J6           -----A-------------AV-S-T--------------V--T------
HC-J8           -----AA------------V---T--------------V----------

                1351                                                1400
HCV-1           PPGSVTVPHPHIEEVALSTTGEIPFYGKAIPLEVIKGGRHLIFCHSKKKC
HCV-H           -------S------------------------------------------
HC-J1           ----I----A-----------------------A---------------
HCV-J           ----I------------H------------I-A---------------
BE8309          ----------------S------------I-------------------
HC-J4.83        --------------IG--NN-----------I-A---------------
HC-J4.91        --------------IG--NN-----------I-A---------------
HCV-CHIHA       ----------------H------------I-A-R---------------
HCV-JTA         ----------------H--------------A---------------
HCV-JTB         ----------------N------------I-------------------
HCV-BK          ----------------H------------I-A-R---------------
HCV-JK1         ----------------PN-------------T---------------
HCV-T           --------------I---N------------I-T---------------
HC-J6           ------T----------GQE-------R----SY---------------
HC-J8           ---T--T--S-------GHE------------AF---------------

                1401                                                1450
HCV-1           DELAAKLVALGIHAVAYYRGLDVSVIPTSGDVVVVATDALMTGYTGDFDS
HCV-H           ------------------------------------S-------F------
HC-J1           ----------V--------------------------------------
HCV-J           -------TG--L------------------------------F------
BE8309          -------SGF--------------------------------F------
HC-J4.83        -------TG--L--------------PI---A----------F------
HC-J4.91        -------TG--L--------------PI-------------F------
HCV-CHIHA       -------SS--L--------------S--------------F------
HCV-JTA         -------SG-----------------------I---------------
HCV-JTB         -------SG----------------------------------------
HCV-BK          -------SG-----------------I--------------------
HCV-JK1         -------S---V-------------------------------------
HCV-T           -------S----H-------------A--H----------F------
HC-J6           -----A-RGM-L---------------Q-------------F------
HC-J8           -----A-RGM-V---------------Q--------------------
```

Figure 6 - continued 1

```
                1451          1465
HCV-1           VIDCNTCVTQTVDFS
HCV-H           ---------------
HC-J1           ---------------
HCV-J           ---------------
BE8309          ---------------
HC-J4.83        ---------------
HC-J4.91        ---------------
HCV-CHINA       ---------------
HCV-JTA         ---------------
HCV-JTB         ---------------
HCV-BK          ---------------
HCV-JK1         ---------------
HCV-T           ---------------
HC-J6           -----VA---V----
HC-J8           -----VA-S-I----
```

Figure 6 - continued 2